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PATENT ABSTRACTS OF JAPAN

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(71)Applicant : YAMANOUCHI PHARMACEUT CO LTD

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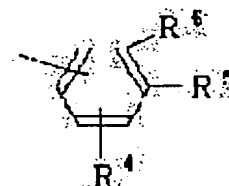
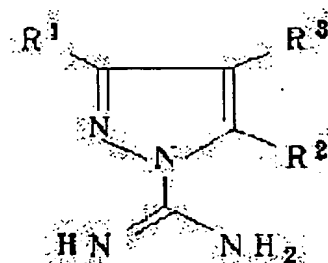
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(54) PYRAZOLE DERIVATIVE

(57)Abstract:

PURPOSE: To obtain a new pyrazole derivative, having inhibiting activity against the Maillard reaction and useful for preventing and/or treating various diabetic complications and diseases due to aging.

CONSTITUTION: The compound is expressed by formula I [R1 and R2 are lower alkyl; R3 is (i) amino which may be substituted with F, NO2, 3C alkyl, lower alkanoyl or lower alkoxy carbonyl, (ii) lower alkyl substituted with halogen, lower alkanoyl, lower alkoxy, lower alkoxy carbonyl or formula II (R4 to R6 are H, NH2, NO2, lower alkyl, lower alkoxy, lower alkoxy carbonyl or aralkyloxy or further R5 and R6 together form lower alkylendioxy) or (iii) carbonyl substituted with any of OH, lower alkyl, aralkyloxy, amine which may be substituted with alkyl or alkoxy which may be substituted with alkoxy or further R2 and R3 together form 3C alkylene], e.g. 3,5-dimethyl-4-propyl-1H-pyrazole-1-carboxamide hydrochloride.



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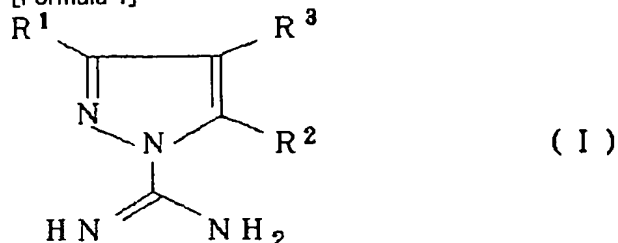
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CLAIMS

[Claim(s)]

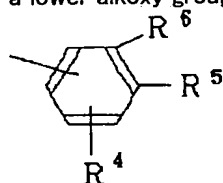
[Claim 1] A general formula (I)

[Formula 1]



(The mark in a formula shows following semantics.)

R1 : Low-grade alkyl group R2 : Low-grade alkyl group R3 : The amino group which may be replaced by (i) fluorine atom, the nitro group, the low-grade alkyl group that is not replaced [with a carbon numbers of three or more], the low-grade alkanoyl radical, or the low-grade alkoxy carbonyl group or (ii) halogen atom, a low-grade alkanoyl radical, a lower alkoxy group, a low-grade alkoxy carbonyl group, and formula [Formula 2]



(5 or R6 : R the same or differing. R4, a hydrogen atom, the amino group, a nitro group, a hydroxyl group, a low-grade alkyl group, a lower alkoxy group, a low-grade alkoxy carbonyl group or an aralkyloxy radical.) Furthermore, R5 and R6 A low-grade alkylene dioxy radical may be formed in one. Low-grade alkyl group replaced by any of the phenyl group shown they are Or (iii) carbonyl group replaced by any of the lower alkoxy group which may be replaced by the hydroxyl-group, low-grade alkyl group, and aralkyloxy radical, the amino group which may be replaced by the low-grade alkyl group, and the lower alkoxy group. Furthermore, R2 R3 A with a carbon numbers of three or more low-grade alkylene group may be formed in one. The pyrazol derivative shown or its salt.

[Translation done.]

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention has the Maillard inhibition activity and relates to a pyrazol derivative useful for the prevention and/or the therapy of a disease by various diabetic complications and aging, or its salt.

[0002] In recent years, a close-up of the denaturation of the protein by the glucose is greatly taken as one of the onset factors of diabetic complications, and it is considered to originate in the Maillard reaction produced in the living body. They are a series of reactions considered to result in an advance glycosylation end product (AGE:Advanced Glycation End Products) with the decomposition for a Maillard reaction to present [the amino group of protein saccharifies nonenzymatic by the glucose (glycosylation), an AMADORI transition product is formed as an initial glycosylation product, glycosylation advances further, and protein constructs a bridge and denaturalizes, and] brown and be refractory, and difficult for it by the protease. or [that advance of the nonenzymatic glycosylation by this reaction or especially generation of AGE protein has a hyperglycemia condition and the slow metabolic rate] — or the protein part which is not metabolized — remarkable — denaturation, depression, and abnormalities of proteins, such as a diabetic's various protein parts, for example, hemoglobin, serum albumin, the collagen and elastin of a connective tissue, myelin, and eyeball RENZUKURISUTARIN It brings and it is thought that it is one of the causes which start the complication of diabetes mellitus, such as a retinopathy, a nephropathy, a cardio-vascular system failure, neuropathy, and a cataract. Moreover, the Maillard reaction in the living body is considered to be one of the mechanisms of aging, and it is guessed that it is what is closely connected also with the disease by aging. Therefore, it is thought very effective in diseases, such as various diabetic complication and a senile disease, to check a Maillard reaction and to control sthenia and AGE generation of nonenzymatic glycosylation, and the development research of the compound which has Maillard reaction inhibition activity conventionally is tried.

[0003] Conventionally, various things are reported as a compound which has the Maillard inhibition activity. For example, the aminoguanidine, alpha-hydrazino histidine, the lysines, and such mixture given in JP,62-142114,A reported for the first time as a Maillard reaction inhibitor are mentioned. These drugs suppose that it is what checks secondary glycosylation, as a result can control protein bridge formation and AGE generation by reacting with the carbonyl portion of the AMADORI transition product which is an initial glycosylation product, and blocking this portion.

[0004]

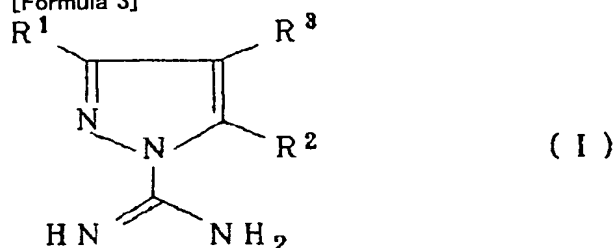
[Problem(s) to be Solved by the Invention] With the conventional Maillard reaction inhibition activity compound, this invention persons completely differed in the chemical structure, invent the pyrazol derivative which has the effect which was excellent as Maillard reaction inhibitor, and came to complete this invention.

[0005]

[Means for Solving the Problem] That is, this invention is a general formula (I).

[0006]

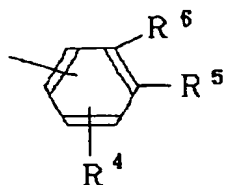
[Formula 3]



[0007] (The mark in a formula shows following semantics.)

R1 : Low-grade alkyl group R2 : Low-grade alkyl group R3 : The amino group which may be replaced by (i) fluorine atom, the nitro group, the low-grade alkyl group that is not replaced [with a carbon numbers of three or more], the low-grade alkanoyl radical, or the low-grade alkoxy carbonyl group or (ii) halogen atom, a low-grade alkanoyl radical, a lower alkoxy group, a low-grade alkoxy carbonyl group, and formula [0008]

[Formula 4]



[0009] (5 or R₆ : R the same or differing. R₄, a hydrogen atom, the amino group, a nitro group, a hydroxyl group, a low-grade alkyl group, a lower alkoxy group, a low-grade alkoxy carbonyl group or an aralkyloxy radical.) Furthermore, R₅ and R₆ A low-grade alkylene dioxy radical may be formed in one. Low-grade alkyl group replaced by any of the phenyl group shown they are Or (iii) carbonyl group replaced by any of the lower alkoxy group which may be replaced by the hydroxyl-group, low-grade alkyl group, and aralkyloxy radical, the amino group which may be replaced by the low-grade alkyl group, and the lower alkoxy group. Furthermore, R₂ R₃ A with a carbon numbers of three or more low-grade alkylene group may be formed in one. They are the pyrazol derivative shown or its salt.

[0010] Hereafter, it explains to details per this invention. In the definition of the general formula of this specification, especially the term that "low-grade" Becomes unless it refuses means the straight chain whose carbon numbers are 1 thru/or six pieces, or the chain of the letter of branching. As a "low-grade alkyl group", a methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, sec-butyl, tert-butyl, a pentyl radical, an isopentyl radical, a neopentyl radical, a tert-pentyl radical, 1-methylbutyl radical, 2-methylbutyl radical, 1, 2-dimethyl propyl group, a hexyl group, an iso hexyl group, etc. are specifically mentioned.

[0011] As a "low-grade alkanoyl radical", a formyl group, an acetyl group, a propionyl radical, a butyryl radical, an isobutyryl radical, a valeryl radical, an iso valeryl radical, a pivaloyl radical, a hexa noil radical, etc. are mentioned. As a "low-grade alkoxy carbonyl group", a methoxycarbonyl group, an ethoxycarbonyl radical, a propoxy carbonyl group, an isopropoxycarbonyl radical, a butoxycarbonyl radical, an iso butoxycarbonyl radical, a sec-butoxycarbonyl radical, a tert-butoxycarbonyl radical, a pentyl (amyl) oxy-carbonyl group, an isopentyl (amyl) oxy-carbonyl group, a hexyloxy carbonyl group, an iso hexyloxy carbonyl group, etc. are mentioned. As a "lower alkoxy group", a methoxy group, an ethoxy radical, a propoxy group, an isopropoxy group, a butoxy radical, an iso butoxy radical, a sec-butoxy radical, a tert-butoxy radical, a pentyloxy (amyloxy) radical, an isopentyloxy radical, a tert-pentyloxy radical, a neopentyl oxy-radical, 2-methyl propoxy group, 1, 2-dimethyl propoxy group, 1-ethyl propoxy group, a hexyloxy radical, etc. are mentioned.

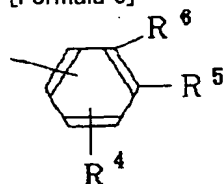
[0012] As an "aralkyloxy radical", it is a phenyl lower alkoxy group preferably, is specifically a benzyloxy radical, a phenethyloxy radical, a phenyl propoxy group, a phenyl butoxy radical, a phenyl pentyloxy radical, a phenyl hexyloxy radical, etc., and is a benzyloxy radical suitably. As a "low-grade alkylene dioxy radical", it is the radical which the oxo-radical combined with the both ends of low-grade alkylene, and a methylene dioxy radical (-OCH₂ O-), an ethylene dioxy radical (-O(CH₂)₂ O-), a propylene dioxy radical, etc. are mentioned. As "a with a carbon numbers of three or more low-grade alkylene group", it is desirable, and the alkylene groups whose carbon numbers are 3 thru/or six pieces are a propylene radical, a tetramethylen radical, 1-methyl trimethylene radical, 2-methyl trimethylene radical, 3-methyl trimethylene radical, ethyl ethylene, dimethyl ethylene, a pentamethylene radical, a methyl tetramethylen radical, a dimethyl trimethylene radical, a pentamethylene radical, a hexamethylene radical, etc., and, specifically, are a propylene radical, a tetramethylen radical, and a pentamethylene

[0013] A fluorine atom, a chlorine atom, a bromine atom, etc. are suitable for a "halogen atom." R₃ It sets, and as (i) "the low-grade alkyl group which is not replaced [with a carbon numbers of three or more]", among said low-grade alkyl groups, a carbon number is the alkyl group which are 3 thru/or six pieces, and are specifically a propyl group, butyl, an isobutyl radical, a pentyl radical, and a hexyl group. As "an amino group which may be replaced by the low-grade alkanoyl radical or the low-grade alkoxy carbonyl group", the amino group by which said low-grade alkanoyl radical or one low-grade alkoxy carbonyl group other than the amino group was replaced is meant, and they are specifically an acetylamino radical, a propionylamino radical, the butyryl amino group, a methoxycarbonylamino radical, an ethoxycarbonylamino radical, a propoxy carbonylamino radical, etc.

(ii) As a "low-grade alkyl group" of the replaced low-grade alkyl group, a methyl group, an ethyl group, and a propyl group are suitable. The substituent is as aforementioned and a methoxycarbonyl group and an ethoxycarbonyl radical are moreover, specifically suitable for a methoxy group and an ethoxy radical for an acetyl group and a propionyl radical as a "low-grade alkoxy carbonyl group" as a "lower alkoxy group" as a "low-grade alkanoyl radical." Bottom

type [0014]

[Formula 5]



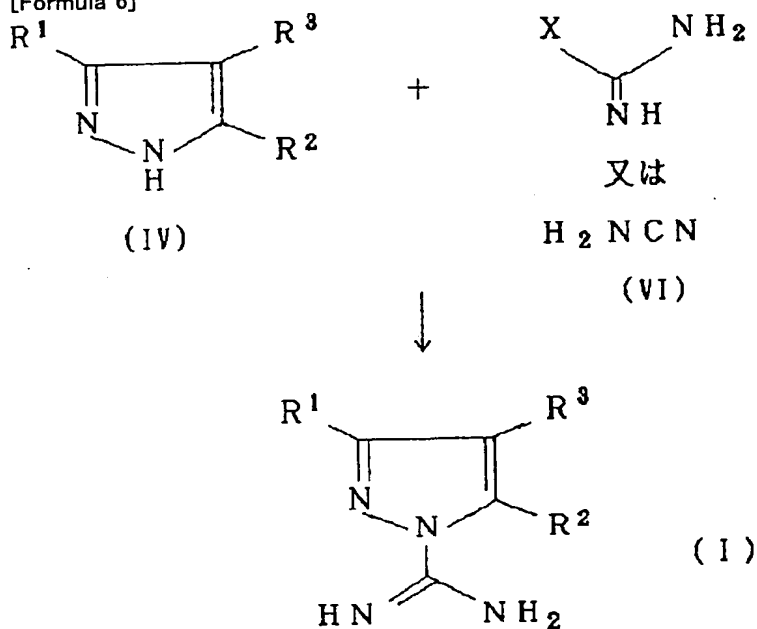
[0015] The inside R₄ of the phenyl group come out of and shown, and R₅ Or R₆ As a "low-grade alkyl group", a "lower alkoxy group", a "low-grade alkoxy carbonyl group", or an "aralkyloxy radical", it is as aforementioned.

(iii) Among the substituents of the replaced carbonyl group, as "an amino group which may be replaced by the low-grade alkyl group", the amino group by which said one low-grade alkyl group other than the amino group was replaced is meant, and, specifically, they are a methylamino radical, an ethylamino radical, a propylamino radical, a butylamino radical, and a pentylamino radical. As "a lower alkoxy group which may be replaced by the lower alkoxy group", the radical by which the lower alkoxy group was replaced by the location of the arbitration of a lower alkoxy group other than said lower alkoxy group is meant, and a methoxyethoxy radical and an ethoxy ethoxy radical are suitable. this invention compound (I) forms an acid and a salt. As a salt with this acid, an acid addition salt with organic acids, such as a mineral acid with a hydrochloric acid, a hydrobromic acid, iodine hydro acid, a sulfuric acid, a nitric acid, and a phosphoric acid, a formic acid and an acetic acid, a propionic acid, oxalic acid, a malonic acid, a succinic acid, boletic acid, a maleic acid, a lactic acid, a malic acid, a citric acid, a tartaric acid, carbonic acid, a picric acid, methansulfonic acid, ethane sulfonic acid, and glutamic acid, can be mentioned. Furthermore, isolation of this invention compound (I) may be carried out as material of a hydrate, solvates, such as ethanol, or a crystal polymorphism, and these invention is also included in this invention.

(Manufacturing method) this invention compound can be manufactured with the application of various synthesis methods. Below, the typical manufacturing method is illustrated.

The first process [0016]

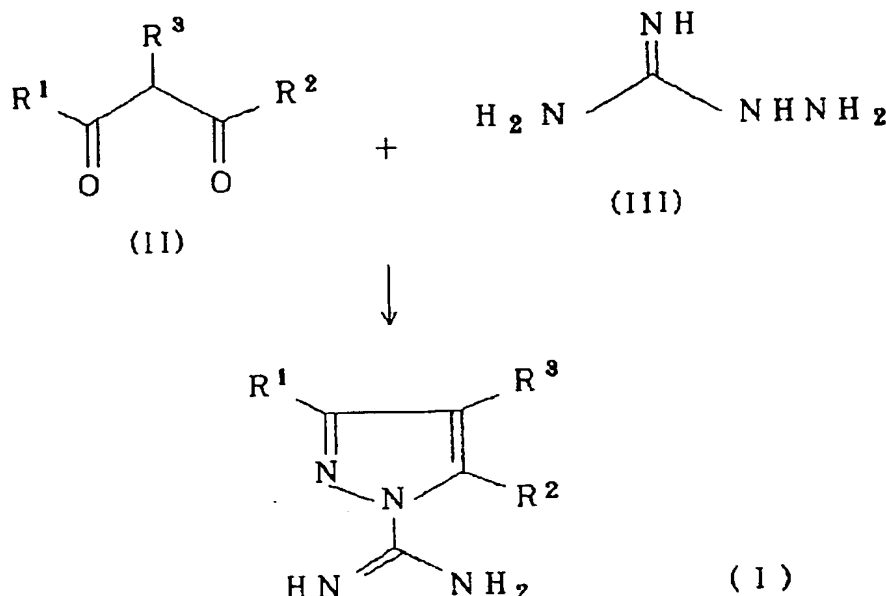
[Formula 6]



[0017] (The mark R^1 in a formula, R^2 , or R^3 is as aforementioned.) X means a halogen. A chlorine atom, a bromine atom, etc. are mentioned as a halogen atom in X . By the halogeno HORUMU amidine salts or the cyanamide (IV) shown by the pyrazole compound shown by the general formula (II), and the general formula (III), this invention compound (I) performs N-amidino-ized reaction, and is manufactured. this reaction — the halogeno HORUMU amidine salts (III) or the cyanamide (IV) of a pyrazole compound (II) and its reaction equivalent amount — the inside of a solvent — warming — it is carried out the bottom thru/or under heating reflux. As a solvent, benzene, a tetrahydrofuran (THF), chloroform, ethyl acetate, toluene, 1,4-dioxane, etc. are mentioned. When using a cyanamide, as for a pyrazole compound (II), it is desirable to use acid addition salts, such as a hydrochloric acid, bromate, or a nitric acid.

The second process [0018]

[Formula 7]



(The mark R1 in a formula, R2, and R3 show above semantics.) By the diketone compound shown by the general formula (V), and aminoguanidine salts (VI), this invention compound (I) performs a ring closure reaction, and is manufactured. this reaction — the aminoguanidine salts (VI) of a diketone compound (V) and its reaction equivalent amount — warming under the room temperature in a solvent — it is carried out in the bottom. As a solvent, water, a methanol, ethanol, a tetrahydrofuran (THF), 1,4-dioxane, etc. are mentioned. A hydrochloride, a bromate salt, or a nitrate is mentioned as an acid addition salt of aminoguanidine.

The third process (nitration reaction)

Inside R3 of this invention compound shown by the general formula (I) What is a nitro group is manufactured by the nitration reaction of a conventional method. For example, R3 The nitration reagent of this invention compound which is a hydrogen atom, its reaction equivalent amount, or an excessive amount is agitated under ice-cooling among an inert solvent thru/or a room temperature, and it is R3. The compound which is a nitro group can be obtained. As an inert solvent, an acetonitrile, an acetic acid, etc. are desirable.

The fourth process (reduction reaction)

Inside R3 of this invention compound shown by the general formula (I) What is an amino group is R3. It is manufactured by returning the compound which is a nitro group. This reduction reaction is performed to the bottom of ordinary pressure thru/or pressurization under existence of the precious metal catalyst of palladium carbon, platinum oxide, etc. by catalytic reduction in solvents usually used for catalytic reduction, such as a methanol, ethanol, and ethyl acetate, that what is necessary is just to follow a conventional method.

Inside R3 of this invention compound shown by the fifth process general formula (I) What is a carboxylic acid is manufactured by removing the benzyl of a benzyl ester compound. That what is necessary is just to follow the fourth above-mentioned process, the removal method of benzyl is hydrogenation and is easily removed by processing by the usual hydrogenation methods, such as a methanol, ethanol, and ethyl acetate, under existence of the precious metal catalyst of palladium carbon, platinum oxide, etc.

[0019]

[Effect of the Invention] this invention compound (I) or its salt has Maillard reaction inhibition activity, and is useful for the prevention and/or the therapy of arteriosclerosis, the arthrosclerosis, etc. which are considered that cardio-vascular system failures, such as various diabetic complications, for example, a retinopathy, a nephropathy, a coronary artery nature heart disease, peripheral circulatory disturbance, and cerebrovascular disease, the diabetes-mellitus sexual nerosis, a cataract, and a Maillard reaction are involving. Moreover, prevention of the atherosclerosis and the senile cataract which are considered to cause by aging of protein, or cancer, and/or the usefulness as a remedy are also expected. Furthermore, since it is also possible to prevent protein bridge formation of a collagen, an elastin, etc., it can also consider as cosmetics or skin external preparations. It is common knowledge that the Maillard reaction relates to deterioration of the protein of not only in the living body but ingesta or a taste object and amino acid, and this invention compound can be used only as functional food for said physic and the cosmetics purpose further again also as Maillard reaction inhibitor of the ingesta containing protein or amino acid, or a taste object.

[0020] (The pharmacology effect) The Maillard reaction inhibition activity of this invention compound is checked by the following experiment methods, and has the outstanding effect.

After having dissolved the Maillard reaction inhibition activity test experiment method lysozyme and the ribose in the 0.1M sodium phosphate buffer solution (pH7.4) containing sodium-azide 3mM so that it might become the concentration of 6mg [ml] /and 100mM(s), respectively, and carrying out incubation for seven days at 37 degrees C, electrophoresis was performed for the constant rate using ejection SDS-PAGE. After electrophoresis,

0.04% Coomassie Brilliant Blue The quantum of the amount of generation of a dimer and a trimer was carried out with the densitometer after dyeing by R-250. It added so that it might be set to 1mM, 3mM, 10mM, or 30mM(s) before an incubation, and the compound of this invention investigated the depressor effect over the dimer and trimer generation in each concentration, and calculated IC50 value.

[0021] (Pharmaceutical preparation—ized matter) The physic constituent which contains one sort, such as this invention compound shown by the general formula (I), or the salt permitted pharmaceutically, a hydrate permitted pharmaceutically, or two sorts or more as an active principle Usually, using the support and the excipient for pharmaceutical preparation which are used, and other additives, it is prepared by a tablet, powder, a fine grain agent, a granule, a capsule, a pill, liquids and solutions, injections, suppositories, ointment, patches, etc., and a medicine is prescribed for the patient taking—orally—wise or parenterally. although the clinical dose to the Homo sapiens of this invention compound is suitably determined in consideration of a patient's symptom, weight, age, sex, etc. which are applied — usually — an adult — per day, in taking orally, it is 10–200mg preferably, and 0.1–500mg is 1 time about this — it is — a medicine is prescribed for the patient in several steps. Since a dose is changed on condition that versatility, an amount smaller than the above—mentioned dose range may be enough as it. A tablet, powder, a granule, etc. are used as a solid—state constituent for internal use by this invention. In such a solid—state constituent, one or the active substance beyond it is mixed with at least one inactive diluent, for example, a lactose, a mannitol, grape sugar, hydroxypropylcellulose, a microcrystal cellulose, starch, a polyvinyl pyrrolidone, and magnesium aluminometasilicate. The constituent may contain a solubilizing agent like additives other than an inactive diluent, for example, lubricant like magnesium stearate and disintegrator like a calcium carboxymethyl cellulose, a stabilizing agent like a lactose, glutamic acid, or an aspartic acid according to a conventional method. The coat of a tablet or the pill may be carried out as occasion demands with the film of stomach solubility, such as cane sugar, gelatin, hydroxypropylcellulose, and hydroxypropylmethylcellulose phthalate, or enteric material.

[0022] The liquid constituent for internal use contains the inactive diluent generally used, for example, purified water, and ethanol including the opacifier permitted in drugs, a solution agent, suspension, syrups, elixirs, etc. This constituent may contain solubilization thru/or a solubilizing agent, a wetting agent, an adjuvant like suspension, a sweetening agent, a flavor agent, an aromatic, and antiseptics in addition to an inactive diluent. As injections for parenteral administration, the sterile solution agent of aqueous or nonaqueous nature, suspension, and an opacifier are included. As a water solution agent and suspension, distilled water for injections and a physiological saline are contained, for example. As the solution agent of nonaqueous solubility, and suspension, there are propylene glycol, a polyethylene glycol, vegetable oil like olive oil, alcohols like ethanol, polysorbate 80 (trade name), etc., for example. Such a constituent may also contain an additive still like an isotonicizing agent, antiseptics, a wetting agent, an emulsifier, a dispersant, a stabilizing agent (for example, lactose), solubilization, or a solubilizing agent. These are sanitized by the combination or the exposure of filtration and a germicide which lets for example, a bacteria hold filter pass. These manufacture a sterile solid—state constituent again, and they can also use it for sterile water or the sterile solvent for injection before use, dissolving. In addition, when preparing the Maillard reaction inhibitor of this invention as cosmetics or skin external preparations, it blends so that 0.05–10 weight section content of this invention compound (I) or its salt may be carried out to the whole pharmaceutical preparation. Cosmetics and skin external preparations can be prepared with a conventional method using a general cosmetics basis or an external use basis. Moreover, the Maillard reaction inhibitor of this invention can also be prepared as ingesta, a taste object, functional food, etc. with a conventional method.

[0023]

[Example] Hereafter, although an example explains this invention to details further, this invention is not limited to these examples. Moreover, this invention compound obtained in the example shows the chemical structure type in the following table.

[0024] In 5ml [of water of 1.56g of example 1 aminoguanidine hydrochlorides], and methanol 30ml, and the solution of 1ml of concentrated hydrochloric acid, the 3-propyl -2 and a solution with a methanol 10ml of 4-2,4-pentanedione 2.06g were added little by little, and were agitated under the room temperature overnight. After it distills off a solvent under reduced pressure and a silica gel chromatography (chloroform: eluate : methanol = 5:1) refines the obtained residue, it recrystallizes from the ethanol-ether, and it is 3 and 5-dimethyl. - 4 - 1.70g of propyl-1H-pyrazole-1-cull BOKISAMIJIN hydrochlorides was obtained.

[0025] physicochemical — description Elemental-analysis value (as nine H17N4 Cl of C)

C(%) H(%) N(%) Cl(%)

Theoretical value 49.88 7.91 25.85 16.36 Experimental value 49.88 7.92 25.97 16.26 nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta:0.88 (3H, t, J= 7Hz) and 1.25– 1.65 (2H, m), 2.20 (3H, s), 2.26–2.49 (2H, m), and 2.45 (3H, s) and 9.30 (4H, brs)

The following examples 2 thru/or the compound of 24 were obtained like the example 1.

[0025] example 24-butyl -3, 5-dimethyl-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound 3-butyl -2, and 4-2,4-pentanedione — physicochemical — description Elemental-analysis value (as C10H19N4 Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 52.05 8.30 24.28 15.36 Experimental value 51.88 8.31 24.29 15.55 nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta:0.80–1.00 (3H, m) and 1.17– 1.60 (4H, m), 2.20 (3H, s), 2.28–2.49 (2H, m), and 2.45 (3H, s) and 9.31 (4H, brs)

[0026] an example 33, the 5-dimethyl-4-(2-methylpropyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw

material compound 3-isobutyl -2, and 4-2,4-pentanedione — physicochemical — description Elemental-analysis value (as C₁₀H₁₉N₄ Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 52.05 8.30 24.28 15.36 Experimental value 51.91 8.24 24.30 15.21 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:0.87 (6H, d, J= 6.6Hz), 1.50-1.85 (1H, m), 2.19 (3H, s), 2.24 (2H, d, J= 8.6Hz), 2.43 (3H, s), 9.26 (4H, brs)

[0027] an example 43, the 5-dimethyl-4-pentyl-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound 3-pentyl -2, and 4-2,4-pentanedione — physicochemical — description Elemental-analysis value (as C₁₁H₂₁N₄ Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 53.98 8.65 22.89 14.48 Experimental value 53.82 8.45 22.91 14.37 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:0.79-0.93 (3H, m) and 1.15- 1.60 (6H, m), 2.20 (3H, s), 2.28-2.48 (2H, m), and 2.43 (3H, s) and 9.26 (4H, brs)

[0028] the example 54-benzyl -3, the 5-dimethyl-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound 3-benzyl -2, and 4-2,4-pentanedione — physicochemical — description Elemental-analysis value (as C₁₃H₁₇N₄ Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 58.98 6.47 21.16 13.39 Experimental value 58.84 6.44 21.21 13.48 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.11 (3H, s), 2.50 (3H, s) and 3.79 (2H, s), and 7.14- 7.31 (5H, m) and 9.31 (4H, brs)

[0029] an example 63, the 5-dimethyl-4-(3-oxo-butyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound 3-acetyl -2, and 6-heptane dione — physicochemical — description Elemental-analysis value (as C₁₀H₁₇N₄ OCl and 0.3H₂ O)

C(%) H(%) N(%) Cl(%)

Theoretical value 48.02 7.09 22.40 14.17 Experimental value 47.87 7.16 22.58 14.33 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.08 (3H, s), 2.21 (3H, s) and 2.43 (3H, s), and 2.48- 2.69 (4H, m) and 9.23 (4H, brs)

[0030] the example 71-amidino -3 and 5-dimethyl-1H-pyrazole-4-methyl propionate hydrochloride raw material compound 4-acetyl-5-oxo-methyl hexanoate — physicochemical — description Elemental-analysis value (as C₁₀H₁₇N₄ O₂ Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 46.07 6.57 21.49 13.60 Experimental value 45.88 6.53 21.51 13.72 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta: — 2.22 (3H, s), 2.43 (3H, s), 2.44-2.77 (4H, m), and 3.59 (3H, s) and 9.25 (4H, brs)

[0031] the example 83-methyl -4, 5 and 6, and a 7-tetrahydro-1H-indazole-1-cull BOKISAMIJIN hydrochloride raw material compound 2-acetyl cyclohexanone — physicochemical — description Elemental-analysis value (as nine H₁₅N₄ Cl of C)

C(%) H(%) N(%) Cl(%)

Theoretical value 50.35 7.04 26.10 16.51 Experimental value 50.27 7.14 26.06 16.29 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:1.67- 1.74 (4H, m), 2.18 (3H, s), 2.37-2.42 (2H, m), and 2.88- 2.91 (2H, m) and 9.16 (4H, brs)

[0032] the example 91-amidino -3 and 5-dimethyl-1H-pyrazole-4-carboxylic-acid methyl hydrochloride raw material compound 2-acetyl methyl acetoacetate — physicochemical — description Elemental-analysis value (as eight H₁₃N₄ of C O₂ Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 41.30 5.63 24.08 15.24 Experimental value 40.90 5.57 24.07 15.16 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.40 (3H, s), 2.72 (3H, s), 3.82 (3H, s), 9.77 (4H, brs)

[0033] the example 101-amidino -3 and 5-dimethyl-1H-pyrazole-4-methyl-acetate hydrochloride raw material compound 3-acetyl-4-oxo-pentanoic acid methyl — physicochemical — description Elemental-analysis value (as nine H₁₅N₄ of C O₂ Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 43.82 6.13 22.71 14.37 Experimental value 43.75 6.05 22.80 14.11 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.18 (3H, s), 2.44 (3H, s), 3.57 (2H, s), 3.63 (3H, s), 9.35 (4H, brs)

[0034] example 113, 5-dimethyl-4-(4-nitrobenzyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound 3-(4-nitrobenzyl)-2, and 4-2,4-pentanedione — physicochemical — description Elemental-analysis value (as C₁₃H₁₆N₅ O₂ Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 50.41 5.21 22.61 11.45 Experimental value 50.07 4.86 22.70 11.45 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.12 (3H, s), 2.51 (3H, s), 3.98 (2H, s), 7.44 (2H, d, J= 8.5Hz), 8.18 (2H, d, J= 8.5Hz), 9.32 (4H, brs)

[0035] example 123, 5-dimethyl-4-(4-methoxybenzyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material

compound 3-(4-methoxybenzyl)-2, and 4-2,4-pentanedione — physicochemical — description Elemental-analysis value (as C₁₄H₁₉N₄ OCl)

C(%) H(%) N(%) Cl(%)

Theoretical value 57.04 6.50 19.01 12.03 Experimental value 56.80 6.48 19.02 12.02 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.10 (3H, s), 2.48 (3H, s) and 3.71 (5H, s), and 6.78- 7.12 (4H, m) and 9.24 (4H, brs)

[0036] the example 131-amidino -3 and a 5-dimethyl-1H-pyrazole-4-carboxylic-acid ethyl hydrochloride raw material compound 2-acetyl ethyl acetoacetate — physicochemical — description Elemental-analysis value (as nine H₁₅N₄ of C O₂ Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 43.82 6.13 22.71 14.37 Experimental value 43.79 6.06 22.87 14.50 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:1.31 (3H, t, J= 7Hz), 2.40 (3H, s), 2.72 (3H, s), 4.28 (2H, q, J= 7Hz), 9.74 (4H, brs)

[0037] the example 141-amidino -3 and 5-dimethyl-1H-pyrazole-4-carboxylic-acid propyl hydrochloride raw material compound 2-acetyl acetoacetic-acid propyl — physicochemical — description Elemental-analysis value (as C₁₀H₁₇N₄ O₂ Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 46.07 6.57 21.49 13.60 Experimental value 45.83 6.85 21.59 13.55 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:0.97 (3H, t, J= 7Hz), 1.69-1.73 (2H, m), 2.40 (3H, s), 2.72 (3H, s), 4.20 (2H, t, J= 6.5Hz), 9.78 (4H, brs)

[0038] the example 151-amidino -3 and 5-dimethyl-1H-pyrazole-4-carboxylic-acid butyl hydrochloride raw material compound 2-acetyl butyl acetoacetate — physicochemical — description Elemental-analysis value (as C₁₁H₁₉N₄ O₂ Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 48.09 6.97 20.39 12.90 Experimental value 47.91 6.95 20.41 12.92 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:0.93 (3H, t, J= 7Hz), 1.37-1.45 (2H, m), 1.65-1.70 (2H, m), 2.40 (3H, s), 2.70 (3H, s), 4.24 (2H, t, J= 6.5Hz), 9.69 (4H, brs)

[0039] the example 161-amidino -3 and 5-dimethyl-1H-pyrazole-4-carboxylic-acid benzyl hydrochloride raw material compound 2-acetyl acetoacetic-acid benzyl — physicochemical — description Elemental-analysis value (as C₁₄H₁₇N₄ O₂ Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 54.46 5.55 18.15 11.48 Experimental value 54.30 5.45 18.28 11.43 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.39 (3H, s), 2.71 (3H, s) and 5.32 (2H, s), and 7.35- 7.47 (5H, m) and 9.76 (4H, brs)

[0040] example 173, 5-dimethyl-4-(3, 4-methylene dioxy benzyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound 3-(3, 4-methylene dioxy benzyl)-2, and 4-2,4-pentanedione — physicochemical — description Elemental-analysis value (as C₁₄H₁₇N₄ O₂ Cl and 0.1H₂ O)

C(%) H(%) N(%)

Theoretical value 54.14 5.58 18.04 Experimental value 53.99 5.57 17.76 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.11 (3H, s), 2.46 (3H, s), 3.69 (2H, s) and 5.96 (2H, s), and 6.61- 6.83 (3H, m) and 9.11 (4H, brs)

[0041] Example 184-(4-benzyloxybenzyl)-3, 5-dimethyl-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound 3-(4-benzyloxybenzyl)-2, 4-2,4-pentanedione nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.10 (3H, s), 2.47 (3H, s), 3.71 (2H, s), 5.06 (2H, s), 6.93 (2H, d, J= 8.5Hz) and 7.06 (2H, d, J= 8.5Hz), and 7.30- 7.43 (5H, m) and 9.17 (4H, brs)

[0042] example 193, 5-dimethyl-4-(4-methoxycarbonyl benzyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound 3-(4-methoxycarbonyl benzyl)-2, and 4-2,4-pentanedione — physicochemical — description Elemental-analysis value (as C₁₅H₁₉N₄ O₂ Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 55.81 5.93 17.36 10.98 Experimental value 55.71 5.86 17.44 11.00 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.10 (3H, s), 2.50 (3H, s), 3.83 (3H, s), 3.89 (2H, s), 7.31 (2H, d, J= 8Hz), 7.89 (2H, d, J= 8Hz), 9.32 (4H, brs)

[0043] example 203, 5-dimethyl-4-(4-hydroxybenzyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound 3-(4-hydroxybenzyl)-2, and 4-2,4-pentanedione — physicochemical — description Elemental-analysis value (as C₁₃H₁₇N₄ OCl)

C(%) H(%) N(%) Cl(%)

Theoretical value 55.61 6.10 19.96 12.63 Experimental value 55.41 6.11 19.89 12.71 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.09 (3H, s), 2.47 (3H, s), 3.65 (2H, s), 6.68 (2H, d, J= 8.3Hz), 6.93 (2H, d, J= 8.3Hz), 9.25 (4H, brs), 9.29 (1H, s)

[0044] example 213, 5-dimethyl-4-(3, 5-dimethyl-4-hydroxybenzyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound 3-(3, 5-dimethyl-4-hydroxybenzyl)-2, and 4-2,4-pentanedione — physicochemical —

description Elemental-analysis value (as C₁₅H₂₁N₄ OCl)

C(%) H(%) N(%) Cl(%)

Theoretical value 58.34 6.85 18.14 11.48 Experimental value 58.12 6.82 18.29 11.47 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.09 (3H, s), 2.10 (6H, s), 2.47 (3H, s), 3.59 (2H, s), 6.66 (2H, s), 8.04 (1H, s), 9.24 (4H, brs)

[0045] example 224-(3, 5-G tert-butyl-4-hydroxybenzyl)-3, 5-dimethyl-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound 3-(3, 5-G tert-butyl-4-hydroxybenzyl)-2, and 4-2,4-pentanedione —

physicochemical — description Elemental-analysis value (as C₂₁H₃₃N₄ OCl and 0.2H₂ O)

C(%) H(%) N(%) Cl(%)

Theoretical value 63.60 8.49 14.13 8.94 Experimental value 63.32 8.38 14.12 9.16 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:1.34 (18H, s), 2.18 (3H, s), 2.49 (3H, s), 3.65 (2H, s), 6.80 (1H, s), 6.90 (2H, s), 9.19 (4H, brs)

[0046] the example 231-amidino -3 and 5-dimethyl-1H-pyrazole-1-carboxylic acid 2-methoxy ethyl hydrochloride raw material compound 2-acetyl acetoacetic acid 2-methoxy ethyl ester — physicochemical — description

Elemental-analysis value (as C₁₀H₁₇N₄ O₃ Cl)

C(%) H(%) N(%) Cl(%)

Theoretical value 43.40 6.19 20.25 12.81 Experimental value 43.11 6.06 20.23 13.02 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.40 (3H, s), 2.71 (3H, s), 3.30 (3H, s), 3.64 (2H, t, J= 4.6Hz), 4.36 (2H, t, J= 4.6Hz), 9.71 (4H, brs)

[0047] The example 241-amidino -3, 5-dimethyl-1H-pyrazole-1-carboxylic acid 2-ethoxyethyl hydrochloride raw material compound 2-acetyl acetoacetic acid 2-ethoxyethyl ester nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:1.12 (3H, t, J= 7Hz), 2.40 (3H, s), 2.72 (3H, s), 3.49 (2H, q, J= 7Hz), 3.67 (2H, t, J= 4.9Hz), 4.34 (2H, t, J= 4.9Hz), 9.73 (4H, brs)

[0048] 1.86g of aminoguanidine hydrochlorides was added to the solution (example 25(1) thoria cetyl methane 3.0g and methanol 30ml) under cooling at -10 degree C, and day churning was carried out under ice-cooling of a reaction mixture. After it distilled off the solvent under reduced pressure and the silica gel chromatography (chloroform: eluate : methanol = 5:1) refined the obtained residue, it recrystallized from ether-chloroform and the 4-acetyl -3 and 5-dimethyl-1H-pyrazole-1-cull BOKISAMIJIN 484mg were obtained.

[0049] Nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

delta:2.38 (3H, s), 2.42 (3H, s), 2.76 (3H, s), 6.54 (3H, brs)

[0050] (2) 0.7ml of 4-N hydrochloric-acid-1,4-dioxane solutions was dropped at the 4-acetyl -3 and a solution (ethanol 1ml and 5-dimethyl-1H-pyrazole-1-cull BOKISAMIJIN 484mg ether 5ml). The depositing crystal is ****(ed) and it is 4-acetyl. - 3 Five - 488mg of dimethyl-1H-pyrazole-1-cull BOKISAMIJIN hydrochlorides was obtained.

元素分析値 (C₈ H₁₃ N₄ C l として)

	C (%)	H (%)	N (%)
理論値	44.35	6.05	25.86
実験値	44.30	6.07	25.67

[0051] physicochemical — description

[0052] Examples 263 and 5 - Ice-cooling and bottom nitronium tetrafluoro PORETO of argon ambient atmosphere 2g were added little by little to the anhydrous acetonitrile 150ml suspension of 2.01g of dimethyl-1H-pyrazole-1-cull BOKISAMIJIN nitrates, and the reaction mixture was agitated for 30 minutes under ice-cooling. A solvent is washed after reduced pressure distilling off, chloroform washes residue, and it is 3 and 5-dimethyl. - 4 - 2.43g of nitro-1H-pyrazole-1-cull BOKISAMIJIN nitrates was obtained.

[0053] Nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

2.77 (3H, s) delta:2.51 (3H, s), 9.83 (4H, brs)

[0054] An example 273, 5-dimethyl -4 - 500mg of palladium carbon was added to the methanol 20ml solution of 984mg of nitro-1H-pyrazole-1-cull BOKISAMIJIN nitrates 10%, and it agitated for 45 minutes under an ordinary pressure hydrogen ambient atmosphere and ice-cooling. After filtering the reaction solution and removing insoluble matter, reduced pressure distilling off of the solvent was carried out. The obtained residue was dissolved in 5ml of water, 160mg of sodium hydroxides was added, and chloroform extracted.

[0055] Reduced pressure distilling off of the solvent was carried out for the organic layer after desiccation with anhydrous sodium sulfate. After dissolving the obtained residue in ethanol 5ml and 2ml of 4-N hydrochloric-acid-1,4-dioxane solutions, reduced pressure distilling off of the solvent was carried out. The obtained residue was *****ed from ethanol-ether-chloroform and the 4-amino -3 and 810mg of 5-dimethyl-1H-pyrazole-1-cull BOKISAMIJIN 2 hydrochlorides were obtained.

[0056] physicochemical — description Elemental-analysis value (as six H₁₃N₅ Cl₂ of C, and 0.5H₂ O)

C(%) H(%) N(%)

Theoretical value 30.65 6.00 29.79 Experimental value 30.74 5.97 30.10 nuclear-magnetic-resonance spectrum (DMSO-d₆, TMS internal standard)

2.62 (3H, s) delta:2.34 (3H, s), 9.58 (7H, brs)

[0057] The following compounds were obtained like example 28 example 27.

4-(4-amino benzyl)-3, the 5-dimethyl-1H-pyrazole-1-cull BOKISAMIJIN 2 hydrochloride raw material compound 3, and a 5-dimethyl-4-(4-nitrobenzyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride — physicochemical — description Elemental-analysis value (as C13H19N5 Cl2 and 0.2H2 O)

C(%) H(%) N(%) Cl(%)

Theoretical value 48.82 6.11 21.90 22.17 Experimental value 48.75 6.12 21.66 22.16 nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

9.25 (3H, brs) delta:2.12 (3H, s), 2.50 (3H, s), 3.54 (2H, brs) and 3.81 (2H, s), 7.24-7.30 (4H, m), 10.31 (2H, brs)

[0058] The solution of 0.3ml of cyanamide 0.17g water was added to the ethanol 5ml solution of 0.46g of example 294-(3-chloropropyl)-3 and 5-dimethyl-1H-pyrazole hydrochlorides, and the reaction mixture was agitated at 80 degrees C on the 1st. Reduced pressure distilling off of the solvent was carried out, the obtained residue was recrystallized from the isopropanol-JIISO pull ether, and 4-(3-chloropropyl)-3 and 0.13g of 5-dimethyl-1H-pyrazole-1-cull BOKISAMIJIN hydrochlorides were obtained.

[0059] Nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta:1.69-2.11 (2H, m), 2.22 (3H, s) and 2.44 (3H, s), 2.48-2.60 (2H, m), and 3.50- 3.11 (2H, m) and 9.27 (4H, brs)

[0060] The following compounds were obtained like example 30 example 29.

3, the 5-dimethyl-4-(3-methoxy propyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound 3, and a 5-dimethyl-4-(3-methoxy propyl)-1H-pyrazole hydrochloride — physicochemical — description — a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta:1.48- 1.78 (2H, m), 2.20 (3H, s), 2.33-2.54 (2H, m), 2.42 (3H, s) and 3.24 (3H, s), and 3.21- 3.35 (2H, m) and 9.22 (4H, brs)

[0061] Example 311-amidino - 3 Five - 10% palladium carbon of the amount of catalysts was added to the methanol 40ml solution of 1.74g of dimethyl-1H-pyrazole-4-carboxylic-acid benzyl hydrochlorides, and it agitated for 15 minutes at the room temperature under the ordinary pressure hydrogen ambient atmosphere. The reaction solution was filtered and reduced pressure distilling off of the solvent was carried out after removing insoluble matter. The obtained residue was recrystallized from the ethanol-ether and the 1-amidino -3 and 1.11g of 5-dimethyl-1H-pyrazole-4-carboxylate acid chloride were obtained.

[0062] physicochemical — description Elemental-analysis value (as seven H11N4 of C O2 Cl, and 0.1H2 O)

C(%) H(%) N(%) Cl(%)

Theoretical value 38.14 5.12 25.42 16.08 Experimental value 38.05 5.01 25.70 16.35 nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

2.72 (3H, s) delta:2.39 (3H, s), 9.76 (4H, brs)

[0063] 32N-butyl of examples 3 Five - 0.49g of KURORU amidine hydrochlorides was added to the solution with a dioxane 30ml of dimethyl-1H-pyrazole-4-carboxamide 0.82g, and the reaction mixture was heated at 100 degrees C for 4 hours. The product was ****(ed) after cooling to the room temperature. The obtained rough crystal was recrystallized from ethanol-diethylether and the N-butyl 1-amidino -3 and 0.54g of 5-dimethyl-1H-pyrazole-4-carboxamide hydrochlorides were obtained.

[0064] physicochemical — description Elemental-analysis value (as C11H20N5 OCl and 0.1H2 O)

C(%) H(%) N(%)

Theoretical value 47.95 7.39 25.41 12.87 Experimental value 47.93 7.31 25.61 12.98 nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

8.10 (1H, t, J= 5.5Hz) delta:0.91 (3H, t, J= 7.3Hz), 1.30-1.36 (2H, m), 1.45-1.52 (2H, m), 2.31 (3H, s) and 2.55 (3H, s), 3.19-3.24 (2H, m), 9.50 (4H, brs)

[0065] The following compounds were obtained like example 33 example 32.

3, 5-dimethyl-4-fluoro - 1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compounds 3 and 5 - Dimethyl-4-fluoro-1H-pyrazole nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

2.47 (3H, d, J= 2.4Hz) delta:2.26 (3H, s), 9.42 (4H, brs)

[0066] Pyridine 5ml was added to the example 344-amino -3 and the dimethylformamide 20ml solution of 0.86g of 5-dimethyl-1H-pyrazole-1-cull BOKISAMIJIN 2 hydrochlorides under ice-cooling, then chlorination valeryl 0.5ml was dropped at them. After agitating a reaction mixture at 4 degrees C overnight, methanol 2ml was added. The residue which was able to obtain the solution after reduced pressure distilling off was diluted with 1-N sodium-hydroxide solution, and chloroform extracted. Reduced pressure distilling off of the solvent was carried out for the organic layer after desiccation with anhydrous sodium sulfate.

[0067] After the silica gel chromatography (chloroform: eluate; methanol = 5:1) refined the obtained residue, it considered as the hydrochloride, it recrystallized from ethanol-diethylether, and 3 and 0.53g of 5-dimethyl-4-pen TANAMIDO-1H-pyrazole-1-cull BOKISAMIJIN hydrochlorides were obtained.

[0068] physicochemical — description Elemental-analysis value (as C11H20N5 OCl)

C(%) H(%) N(%) Cl(%)

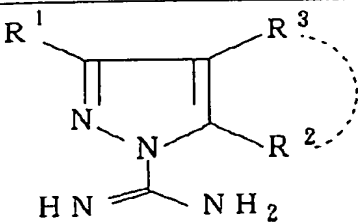
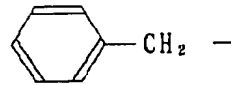
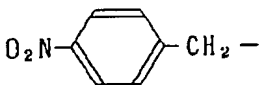
Theoretical value 48.26 7.36 25.58 12.95 Experimental value 48.00 7.27 25.71 13.21 nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta:0.91 (3H, t, J= 7.3Hz), 1.29-1.38 (2H, m), 1.54-1.61 (2H, m), 2.11 (3H, s), 2.32 (2H, t, J= 7.3Hz), 2.34 (3H, s), 9.31 (4H, brs), 9.52 (1H, s)

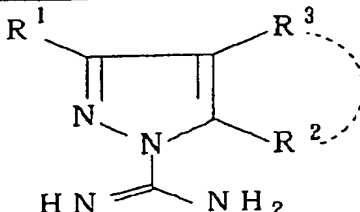

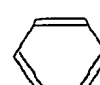
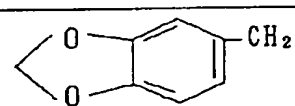
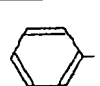
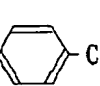


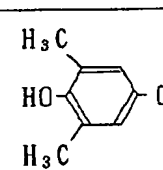
[0069] The following compounds were obtained like example 35 example 34.

3 and 5-dimethyl-4-ethoxycarbonylamino-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound

KURORUGI acid ethyl — physicochemical — description Elemental-analysis value (as nine H16N5 of C O2 Cl)
 C(%) H(%) N(%) Cl(%)
 Theoretical value 41.30 6.16 26.76 13.55 Experimental value 41.07 6.06 26.75 13.56 nuclear-magnetic-resonance
 spectrum (DMSO-d₆, TMS internal standard)
 8.96 (1H, brs) delta:1.20-1.26 (3H, m), 2.14 (3H, s) and 2.36 (3H, s), 4.08-4.13 (2H, m), 9.34 (4H, brs)
 [0070]
 [A table 1]

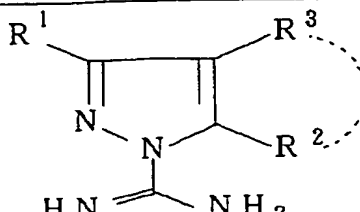
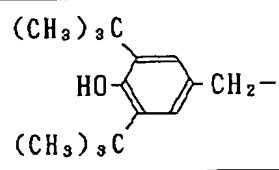

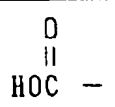
					
実施例	R ¹	R ²	R ³	Salt	理化学的性状
1	CH ₃	CH ₃	CH ₃ (CH ₂) ₂ -	HCl	mp. 204~206 °C Mass180(M-HCl) ⁺
2	CH ₃	CH ₃	CH ₃ (CH ₂) ₃ -	HCl	mp. 193~197 °C Mass194(M-HCl) ⁺
3	CH ₃	CH ₃	(CH ₃) ₂ CHCH ₂ -	HCl	mp. 212~214 °C Mass194(M-HCl) ⁺
4	CH ₃	CH ₃	CH ₃ (CH ₂) ₅ -	HCl	mp. 184~186 °C Mass208(M-HCl) ⁺
5	CH ₃	CH ₃	 -	HCl	mp. 191~195 °C Mass228(M-HCl) ⁺
6	CH ₃	CH ₃	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{C}(\text{CH}_2)_2- \end{array}$	HCl	mp. 151~154 °C Mass208(M-HCl) ⁺
7	CH ₃	CH ₃	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{OC}(\text{CH}_2)_2- \end{array}$	HCl	mp. 145~147 °C Mass224(M-HCl) ⁺
8	CH ₃	-(CH ₂) ₄ -		HCl	mp. 226~228 °C Mass178(M-HCl) ⁺
9	CH ₃	CH ₃	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{OC}- \end{array}$	HCl	mp. 193~196 °C Mass196(M-HCl) ⁺
10	CH ₃	CH ₃	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{OCCH}_2- \end{array}$	HCl	mp. 185~187 °C Mass210(M-HCl) ⁺
11	CH ₃	CH ₃	 -	HCl	mp. 185~188 °C Mass273(M-HCl) ⁺

[0071]
 [A table 2]

					
実施例	R ¹	R ²	R ³	Salt	理化学的性状
12	CH ₃	CH ₃	CH ₃ O-  -CH ₂ -	HCl	mp. 192~194 °C Mass 258 (M-HCl) ⁺
13	CH ₃	CH ₃	CH ₃ CH ₂ OC(=O)-	HCl	mp. 174~176 °C Mass 210 (M-HCl) ⁺
14	CH ₃	CH ₃	CH ₃ (CH ₂) ₂ OC(=O)-	HCl	mp. 146~148 °C Mass 224 (M-HCl) ⁺
15	CH ₃	CH ₃	CH ₃ (CH ₂) ₃ OC(=O)-	HCl	mp. 138~140 °C Mass 238 (M-HCl) ⁺
16	CH ₃	CH ₃	 -CH ₂ OC(=O)-	HCl	mp. 160~162 °C Mass 272 (M-HCl) ⁺
17	CH ₃	CH ₃	 -CH ₂ -	HCl	mp. 181~183 °C Mass 272 (M-HCl) ⁺
18	CH ₃	CH ₃	 -CH ₂ O-  -CH ₂ -	HCl	mp. 197~199 °C Mass 334 (M-HCl) ⁺
19	CH ₃	CH ₃	CH ₃ OC(=O)-  -CH ₂ -	HCl	mp. 183~185 °C Mass 286 (M-HCl) ⁺
20	CH ₃	CH ₃	HO-  -CH ₂ -	HCl	mp. 191~193 °C Mass 244 (M-HCl) ⁺
21	CH ₃	CH ₃	 -CH ₂ -	HCl	mp. 195~197 °C Mass 272 (M-HCl) ⁺

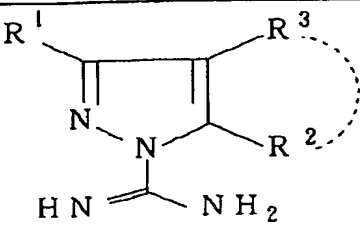
[0072]

[A table 3]

					
実施例	R ¹	R ²	R ³	Salt	理化学的性状
22	CH ₃	CH ₃		HCl	mp. 195~197 °C Mass 356(M-HCl) ⁺
23	CH ₃	CH ₃	CH ₃ O(CH ₂) ₂ OC(=O)-	HCl	mp. 123~125 °C Mass 241(MH-HCl) ⁺
24	CH ₃	CH ₃	CH ₃ CH ₂ O(CH ₂) ₂ OC(=O)-	HCl	mp. 120~122 °C Mass 255(MH-HCl) ⁺
25	CH ₃	CH ₃	CH ₃ C(=O)-	HCl	mp. 164~166 °C Mass 180(M-HCl) ⁺
26	CH ₃	CH ₃	NO ₂	HNO ₃	Mass 183(M-HNO ₃)
27	CH ₃	CH ₃	NH ₂	HCl	mp. 167~169 °C Mass 153(M-2HCl) ⁺
28	CH ₃	CH ₃		2HCl	mp. 213~217 °C Mass 243(M-2HCl) ⁺
29	CH ₃	CH ₃	Cl-(CH ₂) ₃ -	HCl	mp. 183~185 °C Mass: 214, 216(M-HCl) ⁺
30	CH ₃	CH ₃	CH ₃ O(CH ₂) ₃ -	HCl	mp. 155~157 °C Mass 211(MH-HCl) ⁺
31	CH ₃	CH ₃		HCl	mp. 201~203 °C Mass 182(M-HCl) ⁺

[0073]

[A table 4]

					
実施例	R ¹	R ²	R ³	Salt	理化学的性状
32	CH ₃	CH ₃	$\text{CH}_3(\text{CH}_2)_3\text{NHC}-\overset{\text{O}}{\parallel}$	HCl	mp. 182~184 °C Mass 238(MH-HCl) ⁺
33	CH ₃	CH ₃	F	HCl	mp. 168~169 °C Mass 157(MH-HCl) ⁺
34	CH ₃	CH ₃	$\text{CH}_3(\text{CH}_2)_3\text{CNH}-\overset{\text{O}}{\parallel}$	HCl	mp. 178~180 °C Mass 238(MH-HCl) ⁺
35	CH ₃	CH ₃	$\text{CH}_3\text{CH}_2\text{OCNH}-\overset{\text{O}}{\parallel}$	HCl	mp. 193~195 °C Mass 225(M-HCl) ⁺

[Translation done.]

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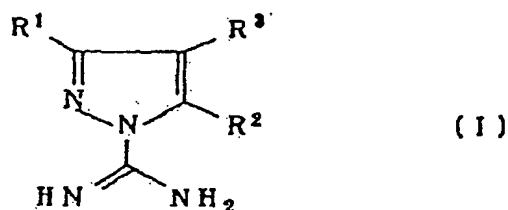
(74) 代理人 弁理士 長井 省三 (外 1 名)

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(54) 【発明の名称】 ピラゾール誘導体

(57) 【要約】 (修正有)

【構成】 下記式 (I)



〔式中、R¹ は低級アルキル基、R² は低級アルキル基、R³ はフッ素原子、ニトロ基、炭素数 3 以上の未置換低級アルキル基、低級アルカノイル基又は低級アルコキシカルボニル基で置換されてもよいアミノ基などを示す〕で示されるピラゾール誘導体又はその塩。

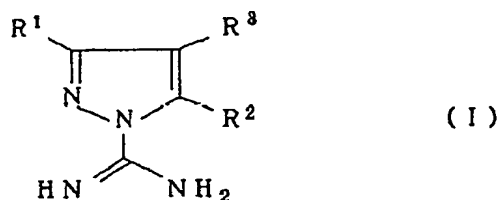
【効果】 メイラード反応を阻害する作用を有し、各種糖尿病合併症、加齢による疾患の予防及び／又は治療に有用である。また、化粧品、皮膚外用剤、飲食物、嗜好物、機能性食品用のメイラード反応阻害剤としても有用である。

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【特許請求の範囲】

【請求項1】 一般式 (I)

【化1】



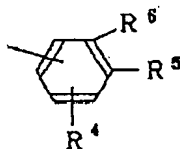
(式中の記号は、以下の意味を示す。)

R¹ : 低級アルキル基R² : 低級アルキル基

R³ : (i) フッ素原子、ニトロ基、炭素数3以上の未置換の低級アルキル基、又は低級アルカノイル基もしくは低級アルコキシカルボニル基で置換されてもよいアミノ基、

又は (ii) ハロゲン原子、低級アルカノイル基、低級アルコキシ基、低級アルコキシカルボニル基及び式

【化2】



(R⁴、R⁵又はR⁶ : 同一又は異なって水素原子、アミノ基、ニトロ基、水酸基、低級アルキル基、低級アルコキシ基、低級アルコキシカルボニル基又はアラルキルオキシ基、更に、R⁴、R⁵が一体となって低級アルキレンジオキシ基を形成してもよい。) で示されるフェニル基の何れかで置換された低級アルキル基、又は (ii) 水酸基、低級アルキル基、アラルキルオキシ基、低級アルキル基で置換されてもよいアミノ基及び低級アルコキシ基で置換されてもよい低級アルコキシ基の何れかで置換されたカルボニル基、更に、R⁴とR⁵とが一体となって炭素数3以上の低級アルキレン基を形成してもよい。) で示されるピラゾール誘導体又はその塩。

【発明の詳細な説明】

【0001】

【産業上の利用分野】 本発明は、メイラード阻害活性を有し、各種糖尿病合併症、加齢による疾患の予防及び/又は治療に有用なピラゾール誘導体又はその塩に関する。

【0002】 近年、グルコースによる蛋白の変性が、糖尿病合併症の発症要因の一つとして大きくクローズアップされてきており、生体内で生ずるメイラード反応に起因するものと考えられている。メイラード反応は、蛋白のアミノ基がグルコースで非酵素的に糖化(グリコシル化)され、初期グリコシル化生成物としてアマドリ転移生成物が形成され、さらにグリコシル化が進行し蛋白が

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架橋し変性して、褐色を呈し難溶でプロテアーゼによる分解が困難な、進行グリコシル化最終生成物(AGE: Advanced Glycation End Products)に至ると考えられている一連の反応である。この反応による非酵素的グリコシル化の進行あるいはAGE蛋白の生成は、特に高血糖状態や代謝速度が遅いかあるいは代謝されない蛋白部位で著しく、糖尿病患者の種々の蛋白部位、例えばヘモグロビン、血清アルブミン、結合組織のコラーゲンやエラスチン、ミエリン、眼球レンズクリスタリンなどの蛋白の変性、機能低下や異常をもたらす、網膜症、腎症、心臓血管系障害、神経障害や白内障などの糖尿病の合併症を惹き起こす原因の一つとなっていると考えられている。また、生体内メイラード反応は、老化の機序の一つと考えられており、加齢による疾患とも密接に関連するものと推測されている。従って、メイラード反応を阻害して非酵素的グリコシル化の亢進やAGE生成を抑制することは、糖尿病の各種合併症や老人性疾患などの疾患に極めて有効であると考えられており、従来よりメイラード反応阻害活性を有する化合物の開発研究が試みられている。

【0003】 従来、メイラード阻害活性を有する化合物としては、種々のものが報告されている。例えば、メイラード反応阻害剤として初めて報告された特開昭62-142114号公報記載のアミノグアニジン、α-ヒドラジノヒスチジン、リジンやこれらの混合物が挙げられる。これらの薬剤は、初期グリコシル化産物であるアマドリ転移生成物のカルボニル部分と反応し、該部分をブロックすることにより、二次グリコシル化を阻害し、ひいては蛋白架橋、AGE生成を抑制できるものであるとしている。

【0004】

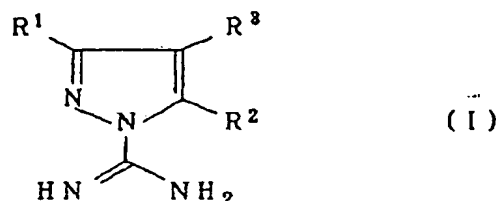
【発明が解決しようとする課題】 本発明者らは、従来のメイラード反応阻害活性化合物とは化学構造を全く異にし、メイラード反応阻害薬としての優れた効果を有するピラゾール誘導体を創製して本発明を完成させるに至った。

【0005】

【課題を解決するための手段】 すなわち、本発明は、一般式 (I)

【0006】

【化3】



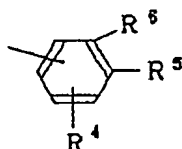
【0007】 (式中の記号は、以下の意味を示す。)

R¹ : 低級アルキル基

R¹ : 低級アルキル基

R¹ : (i) フッ素原子、ニトロ基、炭素数3以上の未置換の低級アルキル基、又は低級アルカノイル基もしくは低級アルコキシカルボニル基で置換されてもよいアミノ基、又は(ii) ハロゲン原子、低級アルカノイル基、低級アルコキシ基、低級アルコキシカルボニル基及び式

【0008】



【0009】(R¹、R¹又はR¹ : 同一又は異なって水素原子、アミノ基、ニトロ基、水酸基、低級アルキル基、低級アルコキシ基、低級アルコキシカルボニル基又はアラルキルオキシ基、更に、R¹、R¹が一体となって低級アルキレンジオキシ基を形成してもよい。)で示されるフェニル基の何れかで置換された低級アルキル基、又は(iii) 水酸基、低級アルキル基、アラルキルオキシ基、低級アルキル基で置換されてもよいアミノ基及び低級アルコキシ基で置換されてもよい低級アルコキシ基の何れかで置換されたカルボニル基、更に、R¹とR¹とが一体となって炭素数3以上の低級アルキレン基を形成してもよい。)で示されるピラゾール誘導体又はその塩である。

【0010】以下、本発明につき詳細に説明する。本明細書の一般式の定義において、特に断わらない限り「低級」なる用語は炭素数が1乃至6個の直鎖又は分岐状の炭素鎖を意味する。「低級アルキル基」としては、具体的には例えばメチル基、エチル基、プロピル基、イソプロピル基、ブチル基、イソブチル基、sec-ブチル基、tert-ブチル基、ペンチル基、イソペンチル基、ネオペンチル基、tert-ペンチル基、1-メチルブチル基、2-メチルブチル基、1,2-ジメチルプロピル基、ヘキシル基、イソヘキシル基等が挙げられる。

【0011】「低級アルカノイル基」としては、ホルミル基、アセチル基、プロピオニル基、ブチリル基、イソブチリル基、バレリル基、イソバレリル基、ピパロイル基、ヘキサノイル基等が挙げられる。「低級アルコキシカルボニル基」としては、メトキシカルボニル基、エトキシカルボニル基、プロポキシカルボニル基、イソプロポキシカルボニル基、ブトキシカルボニル基、イソブトキシカルボニル基、sec-ブトキシカルボニル基、tert-ブトキシカルボニル基、ペンチル(アミル)オキシカルボニル基、イソペンチル(アミル)オキシカルボニル基、ヘキシルオキシカルボニル基、イソヘキシルオキシカルボニル基等が挙げられる。「低級アルコキシ基」としては、メトキシ基、エトキシ基、プロポキシ

基、イソプロポキシ基、ブトキシ基、イソブトキシ基、sec-ブトキシ基、tert-ブトキシ基、ペンチルオキシ(アミルオキシ)基、イソペンチルオキシ基、tert-ペンチルオキシ基、ネオペンチルオキシ基、2-メチルプロポキシ基、1,2-ジメチルプロポキシ基、1-エチルプロポキシ基、ヘキシルオキシ基等が挙げられる。

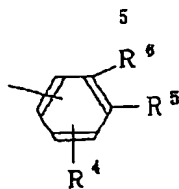
【0012】「アラルキルオキシ基」としては、好ましくはフェニル低級アルコキシ基であり、具体的にはベンジルオキシ基、フェネチルオキシ基、フェニルプロポキシ基、フェニルブトキシ基、フェニルペンチルオキシ基、フェニルヘキシルオキシ基等であり、好適にはベンジルオキシ基である。「低級アルキレンジオキシ基」としては、低級アルキレンの両末端にオキシ基が結合した基であり、メチレンジオキシ基(-OCH₂-O-)、エチレンジオキシ基(-O(CH₂)₂-O-)、プロピレンジオキシ基等が挙げられる。「炭素数3以上の低級アルキレン基」としては、炭素数が3乃至6個のアルキレン基が好ましく、具体的には、プロピレン基、テトラメチレン基、1-メチルトリメチレン基、2-メチルトリメチレン基、3-メチルトリメチレン基、エチルエチレン基、ジメチルエチレン基、ペンタメチレン基、メチルテトラメチレン基、ジメチルトリメチレン基、ペンタメチレン基、ヘキサメチレン基等であり、好適には、プロピレン基、テトラメチレン基、ペンタメチレン基である。

【0013】「ハロゲン原子」は、フッ素原子、塩素原子、臭素原子などが好適である。R¹において(1)「炭素数3以上の未置換の低級アルキル基」としては、前記低級アルキル基のうち炭素数が3乃至6個のアルキル基であり、具体的にはプロピル基、ブチル基、イソブチル基、ペンチル基、ヘキシル基である。「低級アルカノイル基」もしくは低級アルコキシカルボニル基で置換されてもよいアミノ基」としては、アミノ基の他に前記低級アルカノイル基又は低級アルコキシカルボニル基が1個置換されたアミノ基を意味し、具体的にはアセチルアミノ基、プロピオニルアミノ基、ブチリルアミノ基、メトキシカルボニルアミノ基、エトキシカルボニルアミノ基、プロポキシカルボニルアミノ基等である。

(ii) 置換された低級アルキル基の「低級アルキル基」としては、メチル基、エチル基、プロピル基が好適である。またその置換基は前記の通りであり、具体的には「低級アルカノイル基」としてはアセチル基、プロピオニル基が、「低級アルコキシ基」としてはメトキシ基、エトキシ基が、「低級アルコキシカルボニル基」としては、メトキシカルボニル基、エトキシカルボニル基が好適である。下式

【0014】

【化5】



【0015】で示されるフェニル基中 R^1 、 R^2 又は R^3 の「低級アルキル基」、「低級アルコキシ基」、「低級アルコキシカルボニル基」又は「アラルキルオキシ基」としては前記の通りである。

(iii) 置換されたカルボニル基の置換基のうち「低級アルキル基で置換されてもよいアミノ基」としては、アミノ基の他に前記低級アルキル基が1個置換されたアミノ基を意味し、具体的には、メチルアミノ基、エチルアミノ基、プロピルアミノ基、ブチルアミノ基、ペンチルアミノ基である。「低級アルコキシ基で置換されてもよい低級アルコキシ基」としては、前記低級アルコキシ基の他に、低級アルコキシ基の任意の位置に低級アルコキシ基が置換された基を意味し、メトキシエトキシ基、エ

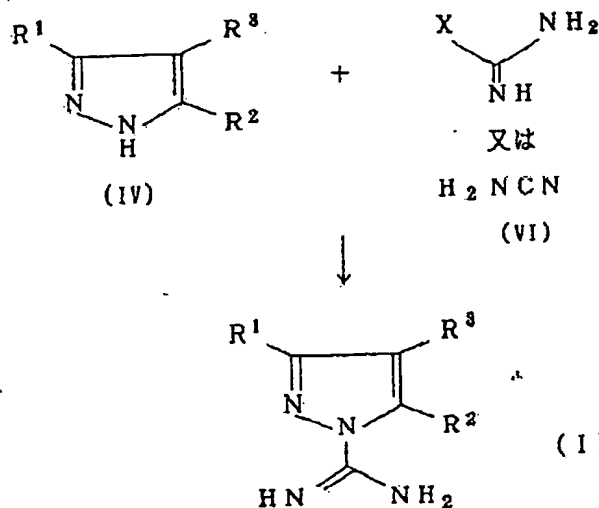
トキシエトキシ基が好適である。本発明化合物(I)は、酸と塩を形成する。かかる酸との塩としては塩酸、臭化水素酸、ヨウ素水素酸、硫酸、硝酸、リン酸との鉍酸や、ギ酸、酢酸、プロピオン酸、シュウ酸、マロン酸、コハク酸、フマル酸、マレイン酸、乳酸、リンゴ酸、クエン酸、酒石酸、炭酸、ピクリン酸、メタンスルホン酸、エタンスルホン酸、グルタミン酸等の有機酸との酸付加塩を挙げることができる。さらに本発明化合物(I)は、水和物や、エタノール等の溶媒和物や結晶多形の物質として単離される場合もあり、本発明にはこれらの発明も含まれる。

(製造法) 本発明化合物は種々の合成法を適用して製造することができる。以下に、その代表的な製造法を例示する。

第一製法

【0016】

【化6】



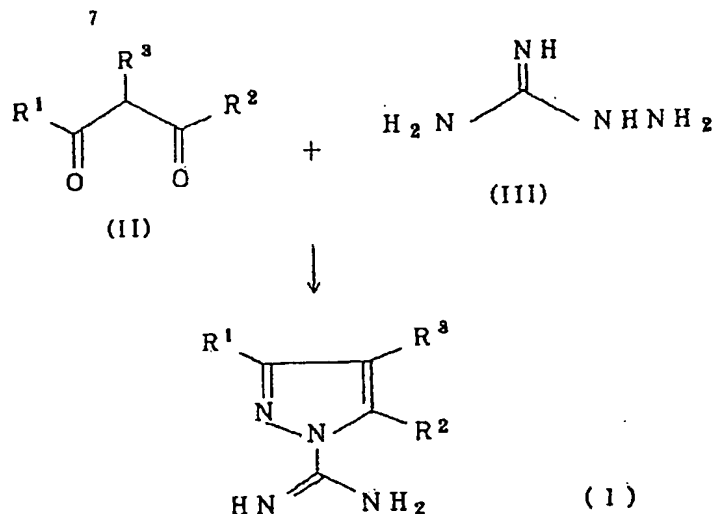
【0017】(式中の記号 R^1 、 R^2 又は R^3 は前記の通りである。Xは、ハロゲンを意味する。)Xにおけるハロゲン原子としては、塩素原子、臭素原子等が挙げられる。本発明化合物(I)は、一般式(II)で示されるピラゾール化合物と一般式(III)で示されるハロゲンホルムアミジン塩類又はシアナミド(IV)とでN-アミジノ化反応を行い製造される。本反応は、ピラゾール化合物(II)とその反応対当量のハロゲンホルムアミジン塩類(III)又はシアナミド(IV)とを溶媒中加温下乃

至加熱還流下で行なわれる。溶媒としては例えばベンゼン、テトラヒドロフラン(THF)、クロロホルム、酢酸エチル、トルエン、1,4-ジオキサン等が挙げられる。シアナミドを使用する場合、ピラゾール化合物(I)は塩酸、臭酸又は硝酸等の酸付加塩を使用することが好ましい。

第二製法

【0018】

【化7】



(式中の記号 R^1 、 R^2 、 R^3 は前記の意味を示す。)
 本発明化合物(I)は一般式(V)で示されるジケトン化合物とアミノグアニジン塩類(VI)とで閉環反応を行い製造される。本反応は、ジケトン化合物(V)とその

第三製法(ニトロ化反応)

一般式(I)で示される本発明化合物のうち R^1 がニトロ基であるものは、常法のニトロ化反応により製造される。例えば、 R^1 が水素原子である本発明化合物とその

第四製法(還元反応)

一般式(I)で示される本発明化合物のうち R^1 がアミノ基であるものは、 R^1 がニトロ基である化合物を還元することにより製造される。本還元反応は、常法に従えばよく、例えば接触還元ではパラジウム炭素、酸化白金などの貴金属触媒の存在下、メタノール、エタノール、酢酸エチル等通常接触還元

第五製法

一般式(I)で示される本発明化合物のうち R^1 がカルボン酸であるものは、ベンジルエステル化合物のベンジル基を除去することにより製造される。ベンジル基の除去法は、前述の第四製法に従えばよく、水素添加で、パラジウム炭素、酸化白金などの貴金属触媒の存在下、メタノール、エタノール、酢酸エチル等通常の水素添加法で処理することにより容易に除去される。

【0019】

【発明の効果】本発明化合物(I)又はその塩は、メイラード反応阻害活性を有し、種々の糖尿病合併症、例えば網膜症、腎症、冠動脈性心疾患や抹消循環障害や脳血管障害などの心臓血管系障害、糖尿病性神経症、白内障やメイラード反応が関与していると考えられている動脈硬化、関節硬化症などの予防及び/又は治療に有用である。また、蛋白の老化によって惹起すると考えられているアテローム性動脈硬化症、老人性白内障や癌の予防及び/又は治療薬としての有用性も期待される。さらに、コラーゲンやエラスチンなどの蛋白架橋を防ぐことも可能であるから、化粧品や皮膚外用剤とすることもできる。さらにまた、メイラード反応が生体内だけでなく、

【0020】(薬理効果)本発明化合物のメイラード反応阻害活性は以下の実験方法によって確認され、優れた効果を有する。

メイラード反応阻害活性試験

実験方法

リゾチームとリボースをアジ化ナトリウム3mMを含む0.1Mリン酸ナトリウム緩衝液(pH7.4)にそれぞれ6mg/ml及び100mMの濃度となるように溶解し、37℃で7日間インキュベーションした後、一定量を取り出しSDS-PAGEを用い、電気泳動を行った。電気泳動後、0.04% Coomassie Brilliant Blue R-250で染色後、

デンシトメーターにより二量体及び三量体の生成量を定量した。本発明の化合物はインキュベーション前に1mM、3mM、10mM又は30mMとなるように添加し、それぞれの濃度における二量体及び三量体生成に対

する抑制効果を調べて、 IC_{50} 値を求めた。

【0021】(製剤化事項)一般式(I)で示される本発明化合物又は製薬学的に許容されるその塩や製薬学的に許容される水和物などの1種又は2種以上を有効成分として含有する医薬組成物は、通常用いられている製剤用の担体や賦形剤、その他の添加剤を用いて、錠剤、散剤、細粒剤、顆粒剤、カプセル剤、丸剤、液剤、注射剤、坐剤、軟膏、貼付剤等に調製され、経口的又は非経口的に投与される。本発明化合物のヒトに対する臨床投与量は適用される患者の症状、体重、年齢や性別等を考慮して適宜決定されるが、通常成人1日当り経口で0.1~500mg、好ましくは10~200mgであり、これを1回であるいは数回に分けて投与する。投与量は種々の条件で変動するので、上記投与量範囲より少ない量で十分な場合もある。本発明による経口投与のための固体組成物としては、錠剤、散剤、顆粒剤等が用いられる。このような固体組成物においては、一つ又はそれ以上の活性物質が、少なくとも一つの不活性な希釈剤、例えば乳糖、マンニトール、ブドウ糖、ヒドロキシプロピルセルロース、微結晶セルロース、デンプン、ポリビニルピロリドン、メタケイ酸アルミン酸マグネシウムと混合される。組成物は、常法に従って、不活性な希釈剤以外の添加剤、例えばステアリン酸マグネシウムのような潤滑剤や纖維素グリコール酸カルシウムのような崩壊剤、ラクトースのような安定化剤、グルタミン酸又はアスパラギン酸のような溶解補助剤を含有していてもよい。錠剤又は丸剤は必要によりショ糖、ゼラチン、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロースフタレートなどの胃溶性あるいは腸溶性物質のフィルムで被膜してもよい。

【0022】経口投与のための液体組成物は、薬剤的に許容される乳濁剤、溶液剤、懸濁剤、シロップ剤、エリキシル剤等を含み、一般的に用いられる不活性な希釈剤、例えば精製水、エタノールを含む。この組成物は不活性な希釈剤以外に可溶化乃至溶解補助剤、湿潤剤、懸濁剤のような補助剤、甘味剤、風味剤、芳香剤、防腐剤を含有していてもよい。非経口投与のための注射剤とし

元素分析値(C, H, N, Clとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	49.88	7.91	25.85	16.36
実験値	49.88	7.92	25.97	16.26

核磁気共鳴スペクトル(DMSO-d₆, TMS内部標準)

δ : 0.88 (3H, t, J=7Hz), 1.25-1.65 (2H, m), 2.20 (3H, s), 2.26-2.49 (2H, m), 2.45 (3H, s), 9.30 (4H, brs)

実施例1と同様にして以下の実施例2乃至24の化合物

元素分析値(C, H, N, Clとして)

	C (%)	H (%)	N (%)	Cl (%)
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ては、無菌の水性又は非水性の溶液剤、懸濁剤、乳濁剤を包含する。水性の溶液剤、懸濁剤としては、例えば注射剤用蒸留水及び生理食塩水が含まれる。非水溶性の溶液剤、懸濁剤としては、例えばプロピレングリコール、ポリエチレングリコール、オリーブ油のような植物油、エタノールのようなアルコール類、ポリソルベート80(商品名)等がある。このような組成物は、さらに等張化剤、防腐剤、湿潤剤、乳化剤、分散剤、安定化剤(例えば、ラクトース)、可溶化乃至溶解補助剤のような添加剤を含んでもよい。これらは例えばバクテリア保留フィルターを通す濾過、殺菌剤の配合又は照射によって無菌化される。これらは又無菌の固体組成物を製造し、使用前に無菌水又は無菌の注射用溶媒に溶解して使用することもできる。なお、本発明のメイラード反応阻害薬を化粧品や皮膚外用剤として調製するときは、本発明化合物(I)又はその塩を製剤全体に対し0.05~10重量部含有するように配合する。化粧品や皮膚外用剤は一般的な化粧品基剤や外用基剤を用いて常法により調製することができる。また、本発明のメイラード反応阻害薬は常法により飲食物、嗜好物、機能性食品などとして調製することもできる。

【0023】

【実施例】以下、実施例により本発明をさらに詳細に説明するが、本発明はこれらの実施例に限定されるものではない。また実施例で得られた本発明化合物は、下表にその化学構造式を示す。

【0024】実施例1

アミノグアニジン塩酸塩1.56gの水5ml、メタノール30ml、濃塩酸1mlの溶液に、3-プロピル-2,4-ペンタンジオン2.06gのメタノール10mlの溶液を少しずつ加え、室温下、一晚攪拌した。溶媒を減圧下留去し、得られた残渣をシリカゲルクロマトグラフィー(溶出液:クロロホルム:メタノール=5:1)で精製した後、エタノール-エーテルより再結晶して、3,5-ジメチル-4-プロピル-1H-ピラゾール-1-カルボキサミジン塩酸塩1.70gを得た。

【0025】理化学的性状

を得た。

【0025】実施例2

4-プロピル-3,5-ジメチル-1H-ピラゾール-1-カルボキサミジン塩酸塩

原料化合物

3-プロピル-2,4-ペンタンジオン

理化学的性状

11

理論値 52.05 8.30

実験値 51.88 8.31

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 0.80-1.00 (3H, m), 1.17-1.60 (4H, m), 2.20 (3H, s), 2.28-2.49 (2H, m), 2.45 (3H, s), 9.31 (4H, brs)

元素分析値 (C₁₁H₁₁N, Clとして)

C (%) H (%) N (%) Cl (%)

理論値 52.05 8.30 24.28 15.36

実験値 51.91 8.24 24.30 15.21

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 0.87 (6H, d, J=6.6 Hz), 1.50-1.85 (1H, m), 2.19 (3H, s), 2.24 (2H, d, J=8.6 Hz), 2.43 (3H, s), 9.26 (4H, brs)

元素分析値 (C₁₁H₁₁N, Clとして)

C (%) H (%) N (%) Cl (%)

理論値 53.98 8.65 22.89 14.48

実験値 53.82 8.45 22.91 14.37

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 0.79-0.93 (3H, m), 1.15-1.60 (6H, m), 2.20 (3H, s), 2.28-2.48 (2H, m), 2.43 (3H, s), 9.26 (4H, brs)

元素分析値 (C₁₁H₁₁N, Clとして)

C (%) H (%) N (%) Cl (%)

理論値 58.98 6.47 21.16 13.39

実験値 58.84 6.44 21.21 13.48

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.11 (3H, s), 2.50 (3H, s), 3.79 (2H, s), 7.14-7.31 (5H, m), 9.31 (4H, brs)

【0029】実施例6

元素分析値 (C₁₁H₁₁N, OCl・0.3H₂Oとして)

C (%) H (%) N (%) Cl (%)

理論値 48.02 7.09 22.40 14.17

実験値 47.87 7.16 22.58 14.33

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.08 (3H, s), 2.21 (3H, s), 2.43 (3H, s), 2.48-2.69 (4H, m), 9.23 (4H, brs)

【0030】実施例7

元素分析値 (C₁₁H₁₁N, O, Clとして)

C (%) H (%) N (%) Cl (%)

12

24.28 15.36

24.29 15.55

【0026】実施例3

3, 5-ジメチル-4-(2-メチルプロピル)-1H-ピラゾール-1-カルボキサミジン塩酸塩

原料化合物

3-イソブチル-2, 4-ペンタンジオン

理化学的性状

【0027】実施例4

3, 5-ジメチル-4-ペンチル-1H-ピラゾール-1-カルボキサミジン塩酸塩

原料化合物

3-ペンチル-2, 4-ペンタンジオン

理化学的性状

【0028】実施例5

4-ベンジル-3, 5-ジメチル-1H-ピラゾール-1-カルボキサミジン塩酸塩

原料化合物

3-ベンジル-2, 4-ペンタンジオン

理化学的性状

3, 5-ジメチル-4-(3-オキソブチル)-1H-ピラゾール-1-カルボキサミジン塩酸塩

原料化合物

3-アセチル-2, 6-ヘプタンジオン

理化学的性状

1-アミノ-3, 5-ジメチル-1H-ピラゾール-4-プロピオン酸メチル塩酸塩

原料化合物

4-アセチル-5-オキソヘキサン酸メチル

理化学的性状

13

14

理論値	46.07	6.57	21.49	13.60
実験値	45.88	6.53	21.51	13.72

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.22 (3H, s), 2.43 (3H, s),
2.44-2.77 (4H, m), 3.59 (3H, s),
9.25 (4H, brs)

【0031】実施例8

元素分析値 (C, H, N, Clとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	50.35	7.04	26.10	16.51
実験値	50.27	7.14	26.06	16.29

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 1.67-1.74 (4H, m), 2.18 (3H, s),
2.37-2.42 (2H, m), 2.88-2.91 (2H, m),
9.16 (4H, brs)

【0032】実施例9

元素分析値 (C, H, N, O, Clとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	41.30	5.63	24.08	15.24
実験値	40.90	5.57	24.07	15.16

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.40 (3H, s), 2.72 (3H, s),
3.82 (3H, s), 9.77 (4H, brs)

【0033】実施例10

元素分析値 (C, H, N, O, Clとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	43.82	6.13	22.71	14.37
実験値	43.75	6.05	22.80	14.11

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.18 (3H, s), 2.44 (3H, s),
3.57 (2H, s), 3.63 (3H, s), 9.35 (4H, brs)

【0034】実施例11

元素分析値 (C, H, N, O, Clとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	50.41	5.21	22.61	11.45
実験値	50.07	4.86	22.70	11.45

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.12 (3H, s), 2.51 (3H, s),
3.98 (2H, s), 7.44 (2H, d, J=8.5 Hz),
8.18 (2H, d, J=8.5 Hz),
9.32 (4H, brs)

【0035】実施例12

元素分析値 (C, H, N, O, Clとして)

	C (%)	H (%)	N (%)	Cl (%)
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3-メチル-4, 5, 6, 7-テトラヒドロ-1H-インダゾール-1-カルボキサミジン塩酸塩

原料化合物

2-アセチルシクロヘキサノン

理化学的性状

1-アミノ-3, 5-ジメチル-1H-ピラゾール-4-カルボン酸メチル塩酸塩

原料化合物

2-アセチルアセト酢酸メチル

理化学的性状

1-アミノ-3, 5-ジメチル-1H-ピラゾール-4-酢酸メチル塩酸塩原料化合物

3-アセチル-4-オキソペンタン酸メチル

理化学的性状

3, 5-ジメチル-4-(4-ニトロベンジル)-1H-ピラゾール-1-カルボキサミジン塩酸塩

原料化合物

3-(4-ニトロベンジル)-2, 4-ペンタンジオン

理化学的性状

3, 5-ジメチル-4-(4-メトキシベンジル)-1H-ピラゾール-1-カルボキサミジン塩酸塩

原料化合物

3-(4-メトキシベンジル)-2, 4-ペンタンジオン

理化学的性状

15		16	
理論値	57.04 6.50	19.01 12.03	
実験値	56.80 6.48	19.02 12.02	
核磁気共鳴スペクトル (DMSO-d ₆ , TMS内部標準)		1-アミノ-3, 5-ジメチル-1H-ピラゾール-4-カルボン酸エチル塩酸塩	
δ: 2.10 (3H, s), 2.48 (3H, s), 3.71 (5H, s), 6.78-7.12 (4H, m), 9.24 (4H, brs)		原料化合物	
【0036】実施例13		2-アセチルアセト酢酸エチル	
		理化学的性状	

元素分析値 (C₁₁H₁₁N₂O₂Clとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	43.82	6.13	22.71	14.37
実験値	43.79	6.06	22.87	14.50

核磁気共鳴スペクトル (DMSO-d ₆ , TMS内部標準)		1-アミノ-3, 5-ジメチル-1H-ピラゾール-4-カルボン酸プロピル塩酸塩	
δ: 1.31 (3H, t, J=7Hz), 2.40 (3H, s), 2.72 (3H, s), 4.28 (2H, q, J=7Hz), 9.74 (4H, brs)		原料化合物	
【0037】実施例14		2-アセチルアセト酢酸プロピル	
		理化学的性状	

元素分析値 (C₁₁H₁₁N₂O₂Clとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	46.07	6.57	21.49	13.60
実験値	45.83	6.85	21.59	13.55

核磁気共鳴スペクトル (DMSO-d ₆ , TMS内部標準)		【0038】実施例15	
δ: 0.97 (3H, t, J=7Hz), 1.69-1.73 (2H, m), 2.40 (3H, s), 2.72 (3H, s), 4.20 (2H, t, J=6.5Hz), 9.78 (4H, brs)		1-アミノ-3, 5-ジメチル-1H-ピラゾール-4-カルボン酸ブチル塩酸塩	
		原料化合物	
		2-アセチルアセト酢酸ブチル	
		理化学的性状	

元素分析値 (C₁₁H₁₁N₂O₂Clとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	48.09	6.97	20.39	12.90
実験値	47.91	6.95	20.41	12.92

核磁気共鳴スペクトル (DMSO-d ₆ , TMS内部標準)		【0039】実施例16	
δ: 0.93 (3H, t, J=7Hz), 1.37-1.45 (2H, m), 1.65-1.70 (2H, m), 2.40 (3H, s), 2.70 (3H, s), 4.24 (2H, t, J=6.5Hz), 9.69 (4H, brs)		1-アミノ-3, 5-ジメチル-1H-ピラゾール-4-カルボン酸ベンジル塩酸塩	
		原料化合物	
		2-アセチルアセト酢酸ベンジル	
		理化学的性状	

元素分析値 (C₁₁H₁₁N₂O₂Clとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	54.46	5.55	18.15	11.48
実験値	54.30	5.45	18.28	11.43

核磁気共鳴スペクトル (DMSO-d ₆ , TMS内部標準)		ンジル)-1H-ピラゾール-1-カルボキサミジン塩酸塩	
δ: 2.39 (3H, s), 2.71 (3H, s), 5.32 (2H, s), 7.35-7.47 (5H, m), 9.76 (4H, brs)		原料化合物	
【0040】実施例17		3-(3, 4-メチレンジオキシベンジル)-2, 4-ペンタンジオン	
3, 5-ジメチル-4-(3, 4-メチレンジオキシベ		理化学的性状	

元素分析値 (C₁₁H₁₁N₁O₁Cl₁・0.1H₂Oとして)

	C (%)	H (%)	N (%)
理論値	54.14	5.58	18.04
実験値	53.99	5.57	17.76

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.11 (3H, s), 2.46 (3H, s),
3.69 (2H, s), 5.96 (2H, s), 6.6
1-6.83 (3H, m), 9.11 (4H, brs)

【0041】実施例18

4-(4-ベンジルオキシベンジル)-3,5-ジメチ
ル-1H-ピラゾール-1-カルボキサミジン塩酸塩

原料化合物

3-(4-ベンジルオキシベンジル)-2,4-ペンタ
ンジオン核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)元素分析値 (C₁₁H₁₁N₁O₁Clとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	55.81	5.93	17.36	10.98
実験値	55.71	5.80	17.44	11.00

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.10 (3H, s), 2.50 (3H, s),
3.83 (3H, s), 3.89 (2H, s), 7.3
1 (2H, d, J=8Hz), 7.89 (2H, d, J
=8Hz), 9.32 (4H, brs)

【0043】実施例20

元素分析値 (C₁₁H₁₁N₁OClとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	55.61	6.10	19.96	12.63
実験値	55.41	6.11	19.89	12.71

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.09 (3H, s), 2.47 (3H, s),
3.65 (2H, s), 6.68 (2H, d, J=8.
3Hz), 6.93 (2H, d, J=8.3Hz),
9.25 (4H, brs), 9.29 (1H, s)

【0044】実施例21

元素分析値 (C₁₁H₁₁N₁OClとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	58.34	6.85	18.14	11.48
実験値	58.12	6.82	18.29	11.47

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.09 (3H, s), 2.10 (6H, s),
2.47 (3H, s), 3.59 (2H, s), 6.6
6 (2H, s), 8.04 (1H, s), 9.24 (4
H, brs)

【0045】実施例22

δ: 2.10 (3H, s), 2.47 (3H, s),
3.71 (2H, s), 5.06 (2H, s), 6.9
3 (2H, d, J=8.5Hz), 7.06 (2H,
d, J=8.5Hz), 7.30-7.43 (5H,
m), 9.17 (4H, brs)

10 【0042】実施例19

3,5-ジメチル-4-(4-メトキシカルボニルベン
ジル)-1H-ピラゾール-1-カルボキサミジン塩酸
塩

原料化合物

3-(4-メトキシカルボニルベンジル)-2,4-ペン
タンジオン

理化学的性状

3,5-ジメチル-4-(4-ヒドロキシベンジル)-
1H-ピラゾール-1-カルボキサミジン塩酸塩

原料化合物

3-(4-ヒドロキシベンジル)-2,4-ペンタンジ
オン

理化学的性状

3,5-ジメチル-4-(3,5-ジメチル-4-ヒド
ロキシベンジル)-1H-ピラゾール-1-カルボキサ
ミジン塩酸塩

原料化合物

3-(3,5-ジメチル-4-ヒドロキシベンジル)-
2,4-ペンタンジオン

理化学的性状

4-(3,5-ジ-tert-ブチル-4-ヒドロキシ
ベンジル)-3,5-ジメチル-1H-ピラゾール-1
-カルボキサミジン塩酸塩

原料化合物

3-(3,5-ジ-tert-ブチル-4-ヒドロキシ
ベンジル)-2,4-ペンタンジオン

50 理化学的性状

元素分析値 (C₁₁H₁₁N₁OCl・0.2H₂Oとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	63.60	8.49	14.13	8.94
実験値	63.32	8.38	14.12	9.16

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 1.34 (18H, s), 2.18 (3H, s),
2.49 (3H, s), 3.65 (2H, s), 6.8
0 (1H, s), 6.90 (2H, s), 9.19 (4
H, brs)

元素分析値 (C₁₁H₁₁N₁O, Clとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	43.40	6.19	20.25	12.81
実験値	43.11	6.06	20.23	13.02

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.40 (3H, s), 2.71 (3H, s),
3.30 (3H, s), 3.64 (2H, t, J=4.
6 Hz), 4.36 (2H, t, J=4.6 Hz),
9.71 (4H, brs)

【0047】実施例24

1-アミジノ-3, 5-ジメチル-1H-ピラゾール-
1-カルボン酸 2-エトキシエチル塩酸塩

原料化合物

2-アセチルアセト酢酸 2-エトキシエチルエステル

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 1.12 (3H, t, J=7 Hz), 2.40 (3
H, s), 2.72 (3H, s), 3.49 (2H,
q, J=7 Hz), 3.67 (2H, t, J=4.9 Hz)
z), 4.34 (2H, t, J=4.9 Hz), 9.7
3 (4H, brs)

【0048】実施例25

(1) トリアセチルメタン3.0gとメタノール30m
lの溶液にアミノグアニジン塩酸塩1.86gを-10
℃に冷却下に加え、反応混合物を氷冷下、一日攪拌した。
溶媒を減圧下留去し、得られた残渣をシリカゲルクロマ
トグラフィー (溶出液: クロロホルム: メタノール=

【0049】核磁気共鳴スペクトル (DMSO-d₆,
TMS内部標準)

δ: 2.38 (3H, s), 2.42 (3H, s),
2.76 (3H, s), 6.54 (3H, brs)

【0050】(2) 4-アセチル-3, 5-ジメチル-
1H-ピラゾール-1-カルボキサミジン484mgの
エタノール1mlとエーテル5mlの溶液に、4N塩酸
-1, 4-ジオキサン溶液0.7mlを滴下した。析出
した結晶をろ取し、4-アセチル-3, 5-ジメチル-

【0046】実施例23

1-アミジノ-3, 5-ジメチル-1H-ピラゾール-

1-カルボン酸 2-メトキシエチル塩酸塩

原料化合物

2-アセチルアセト酢酸 2-メトキシエチルエステル

10 理化学的性状

1H-ピラゾール-1-カルボキサミジン塩酸塩488
mgを得た。

【0051】理化学的性状

元素分析値 (C₈H₁₁N₃Clとして)

	C (%)	H (%)	N (%)
理論値	44.35	6.05	25.86
実験値	44.30	6.07	25.67

【0052】実施例26

3, 5-ジメチル-1H-ピラゾール-1-カルボキサ
ミジン硝酸塩2.01gの無水アセトニトリル150m
lの懸濁液に、氷冷、アルゴン雰囲気下ニトロニウムテ
トラフルオロボレート2gを少しづつ加え、反応混合物
を氷冷下30分間攪拌した。溶媒を減圧留去後、残渣を
クロロホルムで洗浄し、3, 5-ジメチル-4-ニトロ
-1H-ピラゾール-1-カルボキサミジン硝酸塩2.
43gを得た。

【0053】核磁気共鳴スペクトル (DMSO-d₆,
TMS内部標準)

δ: 2.51 (3H, s), 2.77 (3H, s),
9.83 (4H, brs)

【0054】実施例27

3, 5-ジメチル-4-ニトロ-1H-ピラゾール-1
-カルボキサミジン硝酸塩984mgのメタノール20
mlの溶液に10%パラジウム炭素500mgを加え、
常圧水素雰囲気下、氷冷下、45分間攪拌した。反応溶
液を濾過し不溶物を除去した後、溶媒を減圧留去した。
得られた残渣を水5mlに溶解し、水酸化ナトリウム1
60mgを加え、クロロホルムで抽出した。

【0055】有機層を無水硫酸ナトリウムで乾燥後、溶
媒を減圧留去した。得られた残渣をエタノール5mlと
4N塩酸-1, 4-ジオキサン溶液2mlに溶解した
後、溶媒を減圧留去した。得られた残渣をエタノール-
エーテル-クロロホルムから再結晶し、4-アミノ-
3, 5-ジメチル-1H-ピラゾール-1-カルボキサ
ミジン2塩酸塩810mgを得た。

【0056】理化学的性状

元素分析値 (C, H, N, Cl, 0.5H₂Oとして)

	C (%)	H (%)	N (%)
理論値	30.65	6.00	29.79
実験値	30.74	5.97	30.10

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.34 (3H, s), 2.62 (3H, s),
9.58 (7H, brs)

【0057】実施例28

実施例27と同様にして以下の化合物を得た。

元素分析値 (C, H, N, Cl, 0.2H₂Oとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	48.82	6.11	21.90	22.17
実験値	48.75	6.12	21.66	22.16

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.12 (3H, s), 2.50 (3H, s),
3.54 (2H, brs), 3.81 (2H, s),
7.24-7.30 (4H, m), 9.25 (3H, brs),
10.31 (2H, brs)

【0058】実施例29

4-(3-クロロプロピル)-3,5-ジメチル-1H-
ピラゾール塩酸塩0.46gのエタノール5mlの溶
液に、シアナミド0.17gの水0.3mlの溶液を加
え、反応混合物を80℃で1日攪拌した。溶媒を減圧留
去し、得られた残渣をイソプロパノール-ジエチルエ
ーテルより再結晶して、4-(3-クロロプロピル)-
3,5-ジメチル-1H-ピラゾール-1-カルボキサ
ミジン塩酸塩0.13gを得た。

【0059】核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 1.69-2.11 (2H, m), 2.22 (3
H, s), 2.44 (3H, s), 2.48-2.60
(2H, m), 3.50-3.11 (2H, m), 9.
27 (4H, brs)

【0060】実施例30

元素分析値 (C, H, N, O, Cl, 0.1H₂Oとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	38.14	5.12	25.42	16.08
実験値	38.05	5.01	25.70	16.35

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 2.39 (3H, s), 2.72 (3H, s),
9.76 (4H, brs)

【0063】実施例32

N-ブチル 3,5-ジメチル-1H-ピラゾール-4
-カルボキサミド0.82gのジオキサソ30mlの溶

元素分析値 (C, H, N, O, Cl, 0.1H₂Oとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	47.95	7.39	25.41	12.87

4-(4-アミノベンジル)-3,5-ジメチル-1H-
ピラゾール-1-カルボキサミジン2塩酸塩

原料化合物

3,5-ジメチル-4-(4-ニトロベンジル)-1H-
ピラゾール-1-カルボキサミジン塩酸塩

理化学的性状

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実施例29と同様にして以下の化合物を得た。

3,5-ジメチル-4-(3-メトキシプロピル)-1
H-ピラゾール-1-カルボキサミジン塩酸塩

原料化合物

3,5-ジメチル-4-(3-メトキシプロピル)-1
H-ピラゾール塩酸塩

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核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ: 1.48-1.78 (2H, m), 2.20 (3
H, s), 2.33-2.54 (2H, m), 2.42
(3H, s), 3.24 (3H, s), 3.21-3.
35 (2H, m), 9.22 (4H, brs)

【0061】実施例31

1-アミジノ-3,5-ジメチル-1H-ピラゾール-
4-カルボン酸ベンジル塩酸塩1.74gのメタノール
40mlの溶液に、触媒量の10%パラジウム炭素を加
え、常圧水素雰囲気下、室温で15分間攪拌した。反応
溶液をろ過して不溶物を除去後、溶媒を減圧留去した。
得られた残渣をエタノール-エーテルより再結晶して、
1-アミジノ-3,5-ジメチル-1H-ピラゾール-
4-カルボン酸塩1.11gを得た。

【0062】理化学的性状

液に、クロルアミジン塩酸塩0.49gを加え、反応混
合物を100℃で4時間加熱した。室温まで冷却後、生
成物をろ取した。得られた粗結晶をエタノール-ジエチ
ルエーテルより再結晶して、N-ブチル1-アミジノ-
3,5-ジメチル-1H-ピラゾール-4-カルボキサ
ミド塩酸塩0.54gを得た。

【0064】理化学的性状

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実験値 47.93 7.31 25.61 12.98

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ : 0.91 (3H, t, J=7.3 Hz), 1.30-1.36 (2H, m), 1.45-1.52 (2H, m), 2.31 (3H, s), 2.55 (3H, s), 3.19-3.24 (2H, m), 8.10 (1H, t, J=5.5 Hz), 9.50 (4H, brs)

【0065】実施例33

実施例32と同様にして以下の化合物を得た。

3, 5-ジメチル-4-フルオロ-1H-ピラゾール-1-カルボキサミジン塩酸塩

原料化合物

3, 5-ジメチル-4-フルオロ-1H-ピラゾール

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ : 2.26 (3H, s), 2.47 (3H, d, J=2.4 Hz), 9.42 (4H, brs)

元素分析値 (C₁₁H₁₀N₂OClとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	48.26	7.36	25.58	12.95
実験値	48.00	7.27	25.71	13.21

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ : 0.91 (3H, t, J=7.3 Hz), 1.29-1.38 (2H, m), 1.54-1.61 (2H, m), 2.11 (3H, s), 2.32 (2H, t, J=7.3 Hz), 2.34 (3H, s), 9.31 (4H, brs), 9.52 (1H, s)

元素分析値 (C₁₁H₁₁N₂O₂Clとして)

	C (%)	H (%)	N (%)	Cl (%)
理論値	41.30	6.16	26.76	13.55
実験値	41.07	6.06	26.75	13.56

核磁気共鳴スペクトル (DMSO-d₆, TMS内部標準)

δ : 1.20-1.26 (3H, m), 2.14 (3H, s), 2.36 (3H, s), 4.08-4.13

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【0066】実施例34

4-アミノ-3, 5-ジメチル-1H-ピラゾール-1-カルボキサミジン2塩酸塩0.86gのジメチルホルムアミド20mlの溶液に、氷冷下、ピリジン5mlを加え、続いて、塩化バレルル0.5mlを滴下した。反応混合物を4℃で一晩攪拌した後、メタノール2mlを加えた。溶液を減圧留去後、得られた残渣を1N水酸化ナトリウム溶液で希釈して、クロロホルムで抽出した。有機層を無水硫酸ナトリウムで乾燥後、溶媒を減圧留去した。

【0067】得られた残渣をシリカゲルクロマトグラフィー (溶出液: クロロホルム: メタノール=5:1) で精製した後、塩酸塩とし、エタノール-ジエチルエーテルより再結晶して、3, 5-ジメチル-4-ペンタナミド-1H-ピラゾール-1-カルボキサミジン塩酸塩0.53gを得た。

【0068】理化学的性状

【0069】実施例35

実施例34と同様にして以下の化合物を得た。

3, 5-ジメチル-4-エトキシカルボニルアミノ-1H-ピラゾール-1-カルボキサミジン塩酸塩

原料化合物

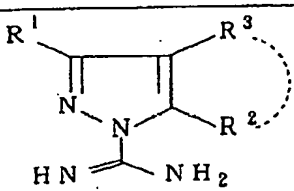
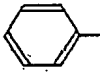
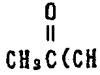
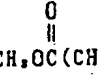
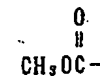
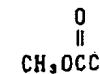
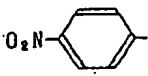
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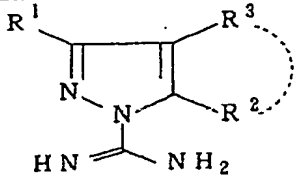


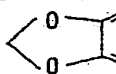




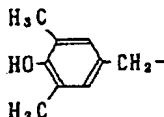
理化学的性状

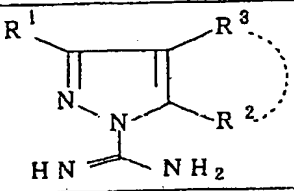
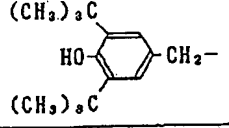

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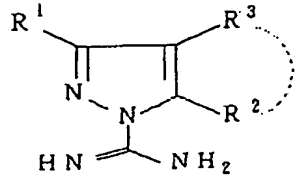
【0070】

【表1】

					
実施例	R ¹	R ²	R ³	Salt	理化学的性状
1	CH ₃	CH ₃	CH ₃ (CH ₂) ₂ -	HCl	mp. 204~206 °C Mass 180(M-HCl) ⁺
2	CH ₃	CH ₃	CH ₃ (CH ₂) ₃ -	HCl	mp. 193~197 °C Mass 194(M-HCl) ⁺
3	CH ₃	CH ₃	(CH ₃) ₂ CHCH ₂ -	HCl	mp. 212~214 °C Mass 194(M-HCl) ⁺
4	CH ₃	CH ₃	CH ₃ (CH ₂) ₃ -	HCl	mp. 184~186 °C Mass 208(M-HCl) ⁺
5	CH ₃	CH ₃	 -	HCl	mp. 191~195 °C Mass 228(M-HCl) ⁺
6	CH ₃	CH ₃	 -	HCl	mp. 151~154 °C Mass 208(M-HCl) ⁺
7	CH ₃	CH ₃	 -	HCl	mp. 145~147 °C Mass 224(M-HCl) ⁺
8	CH ₃	-	-(CH ₂) ₄ -	HCl	mp. 226~228 °C Mass 178(M-HCl) ⁺
9	CH ₃	CH ₃	 -	HCl	mp. 193~196 °C Mass 196(M-HCl) ⁺
10	CH ₃	CH ₃	 -	HCl	mp. 185~187 °C Mass 210(M-HCl) ⁺
11	CH ₃	CH ₃	 -	HCl	mp. 185~188 °C Mass 273(M-HCl) ⁺

					
実施例	R ¹	R ²	R ³	Salt	理化学的性状
12	CH ₃	CH ₃	CH ₃ O-  -CH ₂ -	HCl	mp. 192~194 °C Mass 258 (M-HCl) ⁺
13	CH ₃	CH ₃	CH ₃ CH ₂ OC(=O)-	HCl	mp. 174~176 °C Mass 210 (M-HCl) ⁺
14	CH ₃	CH ₃	CH ₃ (CH ₂) ₄ OC(=O)-	HCl	mp. 146~148 °C Mass 224 (M-HCl) ⁺
15	CH ₃	CH ₃	CH ₃ (CH ₂) ₈ OC(=O)-	HCl	mp. 138~140 °C Mass 238 (M-HCl) ⁺
16	CH ₃	CH ₃	 -CH ₂ OC(=O)-	HCl	mp. 160~162 °C Mass 272 (M-HCl) ⁺
17	CH ₃	CH ₃	 -CH ₂ -	HCl	mp. 181~183 °C Mass 272 (M-HCl) ⁺
18	CH ₃	CH ₃	 -CH ₂ O-  -CH ₂ -	HCl	mp. 197~199 °C Mass 334 (M-HCl) ⁺
19	CH ₃	CH ₃	CH ₃ OC(=O)-  -CH ₂ -	HCl	mp. 183~185 °C Mass 286 (M-HCl) ⁺
20	CH ₃	CH ₃	HO-  -CH ₂ -	HCl	mp. 191~193 °C Mass 244 (M-HCl) ⁺
21	CH ₃	CH ₃	 -CH ₂ -	HCl	mp. 195~197 °C Mass 272 (M-HCl) ⁺

					
実施例	R ¹	R ²	R ³	Salt	理化学的性状
22	CH ₃	CH ₃		HCl	mp. 195~197 °C Mass 356 (M-HCl) ⁺
23	CH ₃	CH ₃	CH ₃ O(CH ₂) ₂ OC(=O)-	HCl	mp. 123~125 °C Mass 241 (MH-HCl) ⁺
24	CH ₃	CH ₃	CH ₃ CH ₂ O(CH ₂) ₂ OC(=O)-	HCl	mp. 120~122 °C Mass 255 (MH-HCl) ⁺
25	CH ₃	CH ₃	CH ₃ C(=O)-	HCl	mp. 164~166 °C Mass 180 (M-HCl) ⁺
26	CH ₃	CH ₃	NO ₂	HNO ₃	Mass 183 (M-HNO ₃)
27	CH ₃	CH ₃	NH ₂	HCl	mp. 167~169 °C Mass 153 (M-2HCl) ⁺
28	CH ₃	CH ₃	H ₂ N-C ₆ H ₄ -CH ₂ -	2HCl	mp. 213~217 °C Mass 243 (M-2HCl) ⁺
29	CH ₃	CH ₃	Cl-(CH ₂) ₃ -	HCl	mp. 183~185 °C Mass: 214, 216 (M-HCl) ⁺
30	CH ₃	CH ₃	CH ₃ O(CH ₂) ₃ -	HCl	mp. 155~157 °C Mass 211 (MH-HCl) ⁺
31	CH ₃	CH ₃		HCl	mp. 201~203 °C Mass 182 (M-HCl) ⁺

					
実施例	R ¹	R ²	R ³	Salt	理化学的性状
32	CH ₃	CH ₃	$\text{CH}_3(\text{CH}_2)_3\text{NHC}-\overset{\text{O}}{\parallel}$	HCl	mp. 182~184 °C Mass 238(MH-HCl) ⁺
33	CH ₃	CH ₃	F	HCl	mp. 168~169 °C Mass 157(MH-HCl) ⁺
34	CH ₃	CH ₃	$\text{CH}_3(\text{CH}_2)_3\text{CNH}-\overset{\text{O}}{\parallel}$	HCl	mp. 178~180 °C Mass 238(MH-HCl) ⁺
35	CH ₃	CH ₃	$\text{CH}_3\text{CH}_2\text{OCNH}-\overset{\text{O}}{\parallel}$	HCl	mp. 193~195 °C Mass 225(M-HCl) ⁺

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